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Archives of Internal Medicine

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CLINICAL STUDIES ON THE RESPIRATION

IX. THE EFFECT OF EXERCISE ON THE METABOLISM, HEART RATE, AND PULMONARY VENTILATION OF NORMAL SUBJECTS AND PATIENTS WITH HEART DISEASE *

FRANCIS W. PEABODY, M.D. AND CYRUS C. STURGIS, M.D.
WITH THE ASSISTANCE OF
BERTHA I. BARKER AND MARGARET N. READ
BOSTON

The investigations described in this paper were undertaken with a view to obtaining further information concerning dyspnea in patients with heart disease. Attention has been directed particularly to the moderate degrees of dyspnea which are incidental to the life of most persons in whom cardiac disease is a limiting, but not an incapacitating lesion, and certain aspects of the respiration and circulation have been studied while the subjects were performing exercises which did not exceed in amount or differ in kind from what they were accustomed to in normal life. The problem has been to determine, so far as possible, the differences in reaction to exercise which account for the fact that patients with heart disease become short of breath as the result of an amount of exercise which does not affect normal persons. It seemed to be important to avoid the complicating factor of muscular fatigue by selecting a type of test exercise which did not involve muscles which the subject was unaccustomed to use, and, since patients with heart disease frequently state that they get out of breath when walking upstairs, it was considered that stair climbing was the form of exercise best adapted to the purposes in view. On account of the complex nature of the observations undertaken, it was necessary for the subject to remain as nearly as possible in one position so that a stair climbing treadmill was made use of. Two groups of subjects, of approximately the same age were studied, one group consisting of eleven normal young men, and the other of eleven young men with valvular heart disease. Unfortunately, such fundamental factors as the circulation rate and minute-volume of cardiac output cannot easily be approached by accurate experimental methods and our observations were, therefore, limited to determinations of the rate, depth, and minute-volume of the respiration, oxygen consumption, carbon dioxid production, and heart rate, before, during, and after a standard amount of exercise.

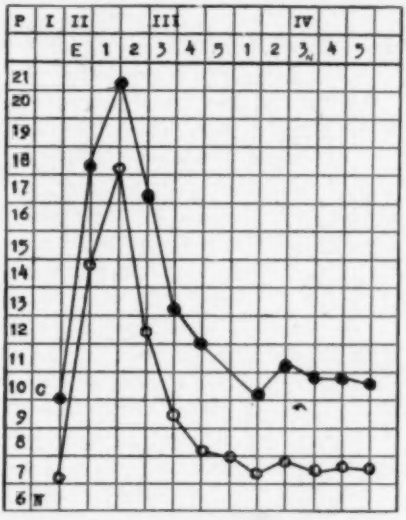
* From the Medical Clinic of the Peter Bent Brigham Hospital.

EXPERIMENTAL PROCEDURE

The experimental procedure was essentially the same in all cases. The subject came to the laboratory at about 9 a. m. after having had his usual breakfast. Electrodes connecting with the electrocardiograph, which was used for counting the heart rate, were attached to his body, and he then sat on a chair, resting, for at least one-half hour. After this a half-mask, covering the nose and mouth, was put in place, carefully tested for leaks, and the subject stepped up on the treadmill. The mask was connected with two rubber tubes of wide bore, one conducting air for inspiration from outdoors, and the other carrying expired air to large Tissot spirometers. Inspired and expired air were separated by rubber flap valves of the type used in gas masks and described by Boothby and Sandiford.[1] A pneumograph, which recorded the respiratory rate on a smoked drum, was adjusted round the chest, and the electrodes were connected to the wires leading to the electrocardiograph. The subject then stood quietly at rest for at least ten minutes more, after which the actual experiment was begun. Each experiment consisted of a series of periods in which the subject was either standing at rest or performing a given amount of exercise. The first period served as a base line for subsequent observations, and in the analysis of the results obtained the percentage variations from the standard resting conditions of this period are reported. In the first period the subject stood quietly at rest for five minutes, during which the expired air was collected, the respiration rate was determined with the pneumograph, and the heart rate was recorded by means of the electrocardiograph. From the data thus obtained the minute-volume of air breathed and the average volume per respiration could be calculated, while analyses of the expired air, with the Haldane portable apparatus, gave the data for calculation of the oxygen consumption and carbon dioxid production. Similar observations were made in each of the subsequent periods. The second period followed the first after about two minutes, during which the necessary technical adjustments were made. In this period the treadmill was started and the subject walked sixty steps upstairs in one minute. The height of each step of the treadmill was 18 cm. At the end of the second period the expired air was immediately shunted into another spirometer and observations were continued without any interval through the third period, during which the subject stood at rest for five minutes, and again through a fourth period of five minutes at rest. During the fourth period all the factors under study were usually essentially the same as they had been before the walk. During the second, third and fourth periods additional observations were made on the volume of air expired for each fifteen

1. Boothby, W. M., and Sandiford, I.: Laboratory Manual of the Technic of Basal Metabolic Rate Determinations, Philadelphia, 1920.

seconds and this proved to be of particular interest in the first minute immediately after the walk. Preliminary experiments showed that, while the amount of exercise in Period II was sufficient to produce dyspnea in the cardiac patients, it did not cause noticeable shortness of breath in the normal subjects. It was considered desirable, however, to make observations on normal persons when they were slightly short of breath and in a condition analogous to that of the cardiac patients at the end of Period II, and this was accomplished without altering the length of walk or number of steps taken, by having them repeat the walk of sixty steps upstairs in one minute while carrying a load consist-



The average ventilation (in liters) per minute of eleven normal individuals and eleven cardiac patients. The figures at the left represent liters. P, period; I standing at rest five minutes, II walking upstairs on a treadmill for one minute, period III standing at rest for five minutes, period IV a second rest period of five minutes. In periods III and IV the readings are recorded for each minute of the period. N, curve of eleven normal individuals; C, curve of eleven cardiac patients; E, point at which exercise began. In the curve of the eleven cardiac patients it was impossible to average the minute-volumes in the fifth minute of the third period, as in five instances the capacity of the spirometer did not permit the expired air to be collected during the fifth minute.

ing of a knapsack weighing 50 pounds on the back. This produced in the normals a degree of dyspnea fairly comparable to that of the cardiac patients in Period II. In the normal subjects, therefore, Period IV was followed by Period V, in which a 50 pound load was carried sixty steps upstairs in one minute, and then by Periods VI and VII, each five minutes long, in which the subjects stood quietly at rest.

In reporting results all volumes of air have been reduced to 0 C. and 760 mm. barometric pressure.

The Subjects—The eleven normal subjects were healthy medical students and doctors. None of them was in particularly good physical training at the time the observations were made, but they represent average specimens of young manhood. The eleven subjects with heart disease

TABLE 1.—VITAL CAPACITY OF NORMAL SUBJECTS AND CARDIAC PATIENTS

No.	Normal Subjects	Age	Height, Cm.	Weight, Kg.	Surface Area,* Sq. M.	Vital Capacity, C.c.	Vital Capacity,† per Cent. of Normal	Diagnosis
1	J. D. T.	31	174.2	86.3	2.01	5,000	100	
2	F. F-S.	25	179.2	69.9	1.88	4,200	90	
3	L. L.	22	179.3	70.4	1.88	4,475	95	
4	H. B.	25	176.6	71.1	1.87	4,900	105	
5	F. W. P.	20	175.2	71.7	1.86	4,400	95	
6	F. R. S.	25	172.2	71.3	1.84	4,700	102	
7	W. E.	26	168.8	69.9	1.80	4,600	102	
8	I. C. S.	27	170.0	67.7	1.78	4,075	96	
9	J. T. L.	24	176.2	61.8	1.76	4,850	110	
10	H. R. M.	25	170.0	65.8	1.76	4,500	102	
11	J. W.	24	179.8	84.1	1.69	5,100	121	
	Cardiac Patients							
1	M. McG.	26	182.2	77.1	1.98	3,550	72	Aortic insufficiency; mitral stenosis and insufficiency; chronic bronchitis
2	F. D.	36	172.2	75.7	1.89	3,900	83	Aortic insufficiency
3	R. G.	24	180.2	68.5	1.88	4,500	96	Aortic insufficiency; mitral stenosis
4	L. I.	25	179.4	64.0	1.82	4,100	90	Aortic and mitral insufficiency
5	F. C.	17	173.4	60.7	1.79	3,600	81	Mitral insufficiency
6	M. B.	25	174.3	57.2	1.68	3,650	87	Pulmonary stenosis
7	C. S.	20	164.7	53.1	1.57	3,300	84	Aortic insufficiency; mitral stenosis and insufficiency
8	B. O.	25	154.0	58.1	1.56	3,400	87	Aortic insufficiency; mitral stenosis and insufficiency
9	A. V.	24	156.8	55.3	1.54	3,650	95	Aortic insufficiency and (?) stenosis; mitral insufficiency
10	E. W.	33	165.9	49.9	1.53	2,275	62	Aortic and mitral insufficiency; (?) mitral stenosis
11	F. K.	25	169.6	48.5	1.49	3,100	83	Aortic insufficiency; mitral stenosis and insufficiency

* DuBois, E. F., and DuBois, D.: Arch. Int. Med. **15**: 868 (July) 1915.
† West, H. F.: Arch. Int. Med. **23**: 366 (March) 1920.

all had valvular lesions but the degree of disability varied greatly from case to case. In some of them dyspnea was scarcely a more prominent symptom than it is in many normal persons, while in others it caused marked limitation of physical exertion. In conformity with previous observations [2] it was found that the degree of tendency to dyspnea was indicated with considerable accuracy by the vital capacity of the lungs.

2. Peabody, F. W., and Wentworth, J. A.: Arch. Int. Med. **20**:443 (Oct.) 1917.

and that the subjects in whom the vital capacity was lowest became most short of breath while walking on the treadmill. With three exceptions the vital capacity of the cardiac patients was below that of all the normals when calculated according to the standards based on body surface area suggested by West.[3] All but one of the patients with heart disease were discharged soldiers and sailors who were ambulatory patients at a Public Health Service hospital, and they were in good general condition, except for their cardiac lesions. They represent very nearly the same age group as the normals, but were on the whole slightly smaller men. The average surface area[4] of the group of normal subjects was 1.83 square meters, while that of the cardiac patients was 1.70 square meters.

Oxygen Consumption.—As an index of the total metabolism of the body the oxygen consumption per square meter of body surface area was determined, and the results are shown in Table 2. In addition to the actual oxygen consumption in cubic centimeters there is also given the percentage variation from the figure in Period I, during which the subject stood at complete rest. This is taken as a base line and considered as 100. In examining the figures in Period I for the two groups it is noticeable that the oxygen consumption of the cardiac patients was slightly more than that of the normals, the average values for each of the two groups being 190 c.c. and 170 c.c., respectively, per square meter. In eight of the cardiac patients the oxygen consumption was over 185 c.c. per square meter, while it was above this figure in only two normals. This difference in the average oxygen consumption of the two groups, while standing at rest, amounts to about 12 per cent. It is quite possible that this small difference has no significance and that it depends on the fact that so limited a number of individuals has been studied, but since this is not certain it is of interest to consider the possible explanations of an increased metabolism in the cardiac patients. Previous observations[5] have shown that the basal metabolism, at complete rest and fasting, of patients with heart disease may be elevated considerably if they are severely decompensated, but that it is within normal limits in persons whose circulation is as well compensated as it was in the subjects of these investigations. Unfortunately, it was not practicable to obtain observations on the metabolism of these individuals when at complete rest and in a fasting state. It seemed possible that in some of the cardiac patients the slightly high metabolism in Period I might be due to nervousness, but in others there was absolutely no reason for considering such a factor, and it is conceivable that the

3. West, H. F.: Arch. Int. Med. **25**:306 (March) 1920.
4. DuBois, D., and DuBois, E. F.: Arch. Int. Med. **15**:868 (July) 1915.
5. Peabody, F. W.; Wentworth, J. A., and Barker, B. I.: Arch. Int. Med. **20**:468 (Oct.) 1917.

TABLE 2.—Oxygen Consumption Per Square Meter of Body Surface Area Per Minute

Normal Subjects	Period I Rest		Period II Exercise		Period III Rest		Period IV Rest		Period V Exercise with Load		Period VI Rest		Period VII Rest	
	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation
J. D. T.	166	100	420	253	290	175	175	105	504	303	308	183	180	108
P. F-S.	125	100	508	406	228	183	136	109	578	463	250	200	148	118
L. L.	171	100	474	277	294	172	187	109	568	332	294	172	185	108
H. B.	157	100	376	239	279	178	170	108	578	368	323	206	163	104
F. W. P.	145	100	445	307	239	165	147	101	585	403	277	191	147	101
P. R. S.	167	100	468	280	239	143	177	106	590	353	*	...	183	110
W. E.	202	100	519	257	301	149	182	90	583	290	347	172	173	86
I. C. S.	181	100	479	265	299	165	185	102	561	310	343	190	177	98
J. T. L.	200	100	605	303	300	150	205	102	694	347	346	173	193	97
H. R. M.	175	100	382	218	291	166	173	99	586	335	345	197	174	99
J. W.	181	100	419	232	263	146	180	100	629	353	337	186	174	96
Average	170	100	463	272	275	162	174	102	588	346	321	189	172	101
Cardiac Patients														
M. McG.	213	100	465	218	269†	126	227	107	...	...	...	...	...	...
F. D.	225	100	526	234	342†	152	223	99	...	...	...	...	...	...
R. G.	198	100	549	284	310†	161	206‡	107	...	...	...	...	...	...
L. T.	155	100	456	294	263	170	167	108	...	...	...	...	...	...
F. C.	172	100	492	286	242	141	162	94	...	...	...	...	...	...
M. R.	170	100	392	231	302†	178	183	108	...	...	...	...	...	...
C. S.	200	100	497	248	247	124	167	84	...	...	...	...	...	...
B. O.	187	100	511	273	307	164	190	102	...	...	...	...	...	...
A. V.	189	100	482	255	341	180	197	104	...	...	...	...	...	...
E. W.	197	100	381	193	374§	190	241	122	...	...	...	...	...	...
F. K.	196	100	513	262	*344	176	218¶	111	...	...	...	...	...	...
Average	190	100	479	252	#	...	198	104	...	...	...	...	...	...

* Gas analysis unsatisfactory in this period.
† 4 minute period.
‡ 4 minute and 30 second period.
§ 3 minute and 30 second period.
¶ 4 minute and 45 second period.
# Average could not be calculated on account of variation in length of periods.

exertion of standing produces a relatively greater increase of metabolism in patients with heart disease than it does in normal persons. It is also possible that the somewhat greater activity of the respiratory muscles, which will be discussed later, accounts for the slightly larger oxygen consumption of the patients with cardiac disease.

The actual oxygen consumption during the walk upstairs (Period II) was also greater in the group of cardiac patients than in the normals, but the average percentage increase in oxygen consumption over that in Period I was somewhat less in the case of patients with heart disease. This difference may be partly due to error inherent in using so short a period, but it was greatly accentuated by subject F. F-S., who had a very low oxygen consumption at rest, and an extraordinarily large percentage increase with exertion. The averages are somewhat misleading, for ten normals had a percentage increase of between 218 and 307, while the cardiac patients had increases between 218 and 294. The difference between the two groups is thus not great. In several instances it was not possible to obtain strictly comparable results for Period III because the minute-volumes of some of the patients with heart disease were so large that the spirometer became filled and the period was only four minutes, or, in one instance, three and one-half minutes long, but, in general, the return to normal on the part of the metabolism, at least as far as can be determined from periods of this length, seemed to proceed at about the same rate in the two groups of subjects. In Period IV the oxygen consumption had returned to approximately what it was before exercise in both groups. It is clear, therefore, that when normal subjects and cardiac patients undertake similar amounts of physical exercise, there is little or no difference in the effect of the exercise on the metabolism in the two groups.

The increase of metabolism among the normals was much greater in Period V, when they walked upstairs with a load on the back, but the return to resting condition was quite rapid and was complete in Period VII.

It is, of course, quite obvious that the periods of exercise, which lasted only one minute, were too short to give accurate information as to the actual oxygen consumption resulting from the work done, and a considerable proportion of the increased consumption fell in Period III, but the results are comparable in the two groups and they do not show any striking difference in behavior.

Carbon Dioxid Production.—In Table 3 the figures for carbon dioxid production in each period are reported. They follow closely the changes already mentioned for oxygen consumption, but it is worthy of note that the return to resting conditions after exercise was less complete in the case of the carbon dioxid production.

TABLE 3.—Carbon Dioxid Production Per Square Meter of Body Surface Area Per Minute.

Normal Subjects	Period I Rest		Period II Exercise		Period III Rest		Period IV Rest		Period V Exercise with Load		Period VI Rest		Period VII Rest	
	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation
J. D. T.	148	100	358	242	299	202	171	116	420	284	328	222	173	117
F. F-S.	105	100	374	356	212	202	118	112	448	427	231	220	128	122
L. L.	142	100	324	228	200	183	166	117	411	289	282	199	161	113
H. B.	124	100	250	202	222	179	149	120	449	362	306	247	156	126
F. W. P.	130	100	337	259	226	174	139	107	402	355	288	221	134	103
F. R. S.	114	100	324	284	205	180	144	126	433	380	*	...	161	141
W. E.	107	100	340	204	261	156	155	98	411	246	322	193	155	96
I. C. S.	157	100	375	239	272	173	170	108	475	303	336	214	167	106
J. T. L.	169	100	448	265	278	165	180	107	535	317	347	205	173	102
H. R. M.	151	100	261	173	256	170	151	100	428	283	360	238	159	105
J. W.	140	100	329	235	205	146	144	103	471	336	302	216	150	107
Average	141	100	338	240	245	174	153	109	449	319	310	220	156	111
Cardiac Patients														
M. McG.	182	100	373	205	355†	195	205	113	...	...	...	...	...	...
F. D.	204	100	414	203	353†	173	248	122	...	...	...	...	...	...
R. G.	189	100	471	249	332†	176	206‡	107	...	...	...	...	...	...
L. I.	125	100	337	270	237	190	140	112	...	...	...	...	...	...
F. C.	139	100	356	256	200	144	136	98	...	...	...	...	...	...
M. R.	142	100	301	212	280†	197	162	114	...	...	...	...	...	...
C. S.	158	100	391	247	225	142	135	85	...	...	...	...	...	...
B. O.	153	100	396	259	264	172	160	105	...	...	...	...	...	...
A. V.	158	100	358	227	325	206	172	109	...	...	...	...	...	...
E. W.	172	100	369	215	379§	220	219	127	...	...	...	...	...	...
F. K.	161	100	343	213	329	204	218¶	135	...	...	...	...	...	...
Average	162	100	374	231	#	...	182	112	...	...	...	...	...	...

* Gas analysis unsatisfactory in this period.
† 4 minute period.
‡ 4 minute and 30 second period.
§ 3 minute and 30 second period.
¶ 4 minute and 45 second period.
# Average could not be calculated on account of variation in length of periods.

TABLE 4.—Percentage of Oxygen Absorbed from Inspired Air and Carbon Dioxid Excreted in Expired Air

Normal Subjects	Period I Rest		Period II Exercise		Period III Rest		Period IV Rest		Period V Exercise with Load		Period VI Rest		Period VII Rest	
	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid
J. D. T.	3.99	3.56	5.08	4.33	4.15	4.28	3.88	3.79	5.13	4.28	4.27	4.63	3.92	3.77
F. F-S.	4.09	3.44	6.16	4.53	4.52	4.20	4.14	3.60	6.07	4.70	4.55	4.20	4.28	3.69
L. L.	4.22	3.50	6.20	4.24	4.58	4.05	4.07	3.61	6.21	4.49	4.50	4.31	4.10	3.57
H. B.	3.91	3.10	4.80	3.19	4.67	3.72	3.74	3.26	4.89	3.80	4.01	3.81	3.19	3.04
F. W. P.	3.99	3.57	3.55	4.21	4.06	3.83	3.64	3.44	5.46	4.31	3.88	4.04	3.66	3.30
F. R. S.	4.24	2.90	5.00	3.47	3.69	3.16	3.96	3.23	5.06	3.72	....	....	3.12	2.75
W. E.	4.16	3.44	6.26	4.10	4.32	3.74	3.81	3.25	6.03	4.25	4.30*	3.90	3.61	3.24
I. C. S.	5.23	4.56	6.17	4.83	5.28	4.81	4.74	4.35	5.88	4.97	5.28	5.17	4.74	4.47
J. T. L.	5.19	4.38	6.81	5.04	4.75	4.40	4.71	4.13	5.67	4.37	4.23	4.24	4.13	3.69
H. R. M.	4.05	3.49	5.94	4.06	4.50	3.96	3.81	3.33	6.04	4.41	4.04	4.21	3.76	3.44
J. W.	4.98	3.87	5.28	4.14	5.02	3.91	4.34	3.48	6.02	4.44	4.94	4.43	3.98	3.44
Cardiac Patients														
M. McG.	4.38	3.73	5.02	4.03	4.20†	4.04†	3.95	3.57	....	....	....	....	....	....
F. D.	3.67	3.34	4.72	3.72	3.48†	3.59†	2.77	3.05	....	....	....	....	....	....
R. G.	3.13	3.07	4.59	3.94	3.04†	3.25†	2.84‡	2.81‡	....	....	....	....	....	....
L. I.	3.52	2.85	4.73	3.49	3.41	3.07	3.08	2.59	....	....	....	....	....	....
F. C.	4.48	3.62	5.55	4.02	4.83	3.98	4.57	3.82	....	....	....	....	....	....
M. R.	2.89	2.41	3.88	2.98	2.88†	2.67†	2.58	2.28	....	....	....	....	....	....
C. S.	3.25	2.57	4.18	3.29	3.15	2.87	3.12	2.61	....	....	....	....	....	....
B. O.	4.06	3.31	4.48	3.47	3.98	3.42	3.91	3.30	....	....	....	....	....	....
A. V.	3.76	3.14	4.99	3.71	4.22	4.02	3.64	3.17	....	....	....	....	....	....
E. W.	3.38	2.96	2.75	2.66	2.50§	2.53§	2.81	2.56	....	....	....	....	....	....
F. K.	3.16	2.59	4.75	3.18	3.40	3.26	2.53¶	2.53¶	....	....	....	....	....	....

† 4 minute period. ‡ 4 minute and 30 second period. § 3 minute and 30 second period. ¶ 4 minute and 45 second period.

Table 4 gives the percentage of oxygen absorbed from the inspired air and the percentage of carbon dioxid excreted in the expired air. It will be seen that the figures for both are lower in the group of cardiac patients than in the normal subjects. The average percentage of oxygen absorbed by the normals while at rest was 4.36 and during exercise was 5.57, while the corresponding figures for the patients with heart disease were 3.60 and 4.51. These results are of special interest in connection with the observations on the minute-volume of pulmonary ventilation.

TABLE 5.—Respiratory Quotients.

Normal Subjects	Period I Rest	Period II Exercise	Period III Rest	Period IV Rest	Period V Exercise with Load	Period VI Rest	Period VII Rest
J. D. T.	0.80	0.85	1.03	0.98	0.82	1.10	0.96
F. F-S.	0.84	0.74	0.93	0.87	0.77	0.92	0.86
L. L.	0.88	0.68	0.88	0.89	0.91	0.96	0.87
H. B.	0.79	0.67	0.80	0.87	0.78	0.95	0.95
F. W. P.	0.90	0.76	0.94	0.95	0.79	1.04	0.91
F. R. S.	0.68	0.69	0.85	0.82	0.74	*	0.88
W. E.	0.83	0.66	0.87	0.85	0.71	0.93	0.90
I. C. S.	0.87	0.78	0.91	0.92	0.85	0.98	0.94
J. T. L.	0.84	0.74	0.96	0.88	0.77	1.00	0.89
H. R. M.	0.86	0.68	0.88	0.87	0.73	1.04	0.92
J. W.	0.78	0.78	0.78	0.80	0.74	0.90	0.86
Average	0.83	0.73	0.87	0.88	0.78	0.98	0.90
Cardiac Patients							
M. McG.	0.85	0.80	0.96†	0.90	....	....	....
F. D.	0.91	0.79	1.03†	1.05	....	....	....
R. G.	0.98	0.86	1.10†	0.99‡	....	....	....
L. I.	0.81	0.74	0.90	0.84	....	....	....
F. C.	0.81	0.72	0.82	0.84	....	....	....
M. B.	0.88	0.77	0.98†	0.88	....	....	....
C. S.	0.79	0.79	0.91	0.84	....	....	....
B. O.	0.92	0.78	0.86	0.84	....	....	....
A. V.	0.84	0.74	0.95	0.87	....	....	....
E. W.	0.88	0.97	1.00§	0.91	....	....	....
F. K.	0.82	0.67	0.96	1.00¶	....	....	....
Average	0.85	0.78	#	0.90	....	....	....

* Gas analysis unsatisfactory in this period.
† Four minute period.
‡ Four minute and 30 second period.
§ Three minute and 30 second period.
¶ Four minute and 45 second period.
# Average could not be calculated on account of the variation in length of periods.

Respiratory Quotients.—The respiratory quotients (Table 5) are approximately similar for the two groups of subjects in the first rest period. The figures for F. R. S. are low and probably should not be taken into consideration as there would seem to be some technical error involved. In Period II the exercise was associated with a lowering of the quotients in nine of the eleven subjects in each group. This is contrary to the results obtained by Krogh and Lindhard [6] who found a sudden rise in the respiratory quotient at the onset of hard work. Krogh and Lindhard called attention to the fact that this does not represent an altered metabolism but merely a disturbance of the balance between

6. Krogh, A., and Lindhard, J.: J. Physiol. **47**:112, 1913.

ventilation and blood flow, with a proportionally greater increase of pulmonary ventilation. The difference in findings may be due to the very mild character of the exercise performed by the subjects of this investigation. The low quotients during the exercise period indicate an inadequate excretion of carbon dioxid, and this was compensated for by the washing out of carbon dioxid after the cessation of exercise, as is shown by the general tendency to a rise in respiratory quotient in Period III. The same lowering of quotient during exercise and rise of quotient immediately after exercise was seen in the normal subjects in Periods V and VI.

Minute-Volume of Pulmonary Ventilation.—The actual volumes of pulmonary ventilation are given in Table 6, and it is seen that the figures for the first period of standing at rest (Period I) are considerably higher in the group of cardiac patients than in the group of normal subjects. On account of the fact that the cardiac patients were, in general, smaller men than the normal subjects, this difference becomes even more evident when the minute-volume is calculated per square meter of body surface area (Table 7). Nine of the patients with heart disease had a minute-volume of between 4.61 and 6.20 liters per square meter surface area, while eight of the normals had a minute-volume of between 3.63 and 4.33 liters per square meter surface area. The average minute-volume of the cardiac patients was 5.37 liters per square meter surface area, or 37 per cent. higher than the average minute-volume of the normals, which was only 3.90 liters per square meter surface area. The difference between the minute-volumes of the two groups, while standing at rest, was thus much greater than the difference in oxygen consumption which amounted to only 12 per cent. This fact, which is of considerable importance, will be discussed later.

As the result of walking upstairs (Period II) the minute-volume increased in both groups of subjects. It reached a considerably higher level in the patients with heart disease than it did in the normals, but it is striking that the percentage rise over the resting minute-volume (Period I) was approximately the same in the two groups.

In the study of the minute-volume of pulmonary ventilation the most important points are to be gathered from a careful analysis of Period III, the first rest period after the walk upstairs. Practically every subject in both groups stated that he was more conscious of his breathing, or felt more dyspneic, immediately after he stopped walking than he did during the actual exercise. In the light of this statement it is exceedingly interesting to discover that the minute-volume was almost invariably higher in the first minute of rest than it was during the exercise period. This is shown in Tables 6 and 7, in which Period IIa represents the first minute of rest, and also in the chart, in which the minute-volume is plotted for each separate minute in Periods II, III

TABLE 6.—Minute-Volume of Pulmonary Respiration

Normal Subjects	Period I Rest		Period II Exercise		Period IIa *		Period III Rest		Period IV Rest		Period V Exercise with Load		Period Va *		Period VI Rest		Period VII Rest	
	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation
J. D. T.	8.34	100	16.60	200	21.80	262	14.10	169	9.05	108	19 70	236	25.50	306	14.20	170	9.22	111
F. F-S.	5.90	100	15.80	268	18.30	310	9.70	166	6.30	107	18.30	310	19.20	326	10.50	178	6.60	112
L. L.	7.61	100	14.40	189	19.10	250	12.10	159	8.64	114	17.20	226	20.80	273	12.30	162	8.48	111
H. B.	7.50	100	14.70	196	15.50	207	11.20	149	8.52	114	22.10	295	23.50	313	15.00	200	9.57	128
F. W. P.	6.75	100	14.90	221	18.90	280	11.00	163	7.50	111	19.90	295	23.40	347	13.30	197	7.56	112
F. R. S.	7.26	100	17.20	237	20.00	276	11.90	164	8.23	113	21.40	295	26.10	387	22.20†	301	10.80	149
W. E.	8.73	100	14.90	171	20.20	232	12.60	145	8.59	98	17.40	199	24.80	284	14.90	171	8.61	99
I. C. S.	6.15	100	13.80	224	15.90	258	10.10	164	6.96	113	17.00	277	18.10	294	11.60	189	6.63	108
J. T. L.	6.78	100	15.70	232	18.70	276	11.10	164	7.67	113	21.50	307	26.20	386	14.40	212	8.23	121
H. R. M.	7.61	100	11.30	148	18.60	244	11.40	150	7.98	105	17.10	225	25.80	339	15 00	197	8.15	107
J. W.	6.13	100	13.40	218	12.70	207	8.85	144	7.02	115	17.94	292	16.60	271	11.53	188	7.38	120
Average	7.16	100	14.80	207	18.20	254	11.30	158	7.86	100	19.00	265	22.90	320	13.30‡	185	8.29	116
Cardiac Patients																		
M. McG.	9.63	100	18.33	191	26.10	271	17.42§	181	11.37	118	.....	...	.....	...	.....	...	.....	...
F. D.	11.60	100	21.10	182	23.70	204	18.60§	160	13.70	118	.....	...	.....	...	.....	...	.....	...
R. G.	11.60	100	22.50	194	23.00	198	19.20§	166	13.60¶	117	.....	...	.....	...	.....	...	.....	...
L. I.	7.98	100	17.60	220	20.80	261	14.00	176	9.84	123	.....	...	.....	...	.....	...	.....	...
F. C.	6.88	100	15.90	231	17.70	258	6.50	95	6.35	92	.....	...	.....	...	.....	...	.....	...
M. R.	9.87	100	16.97	172	22.60	229	17.60§	178	11.95	121	.....	...	.....	...	.....	...	.....	...
C. S.	9.70	100	18.70	193	19.90	205	12.30	127	8.10	84	.....	...	.....	...	.....	...	.....	...
B. O.	7.19	100	17.80	248	19.40	270	12.02	167	7.56	105	.....	...	.....	...	.....	...	.....	...
A. V.	7.75	100	14.90	192	17.70	228	12.40	160	8.35	108	.....	...	.....	...	.....	...	.....	...
E. W.	8.90	100	21.20	238	27.70	315	22.90#	257	13.10	147	.....	...	.....	...	.....	...	.....	...
F. K.	9.24	100	16.10	174	19.90	215	15.06	163	12.85**	140	.....	...	.....	...	.....	...	.....	...
Average	9.12	100	18.30	201	21.70	238	††	...	10.60	116	.....	...	.....	...	.....	...	.....	...

* First minute of rest after exercise.
† Two minute and 45 second period.
‡ Average does not include figures for F. R. S.
§ Four minute period.
¶ Four minute and 30 second period.
# Three minute and 30 second period.
** Four minute and 45 second period.
†† Average could not be calculated on account of variation in length of periods.

TABLE 7.—Minute-Volume of Pulmonary Ventilation Per Square Meter of Body Surface Area.

Normal Subjects	Period I Rest		Period II Exercise		Period IIa *		Period III Rest		Period IV Rest		Period V Exercise with Load		Period Va *		Period VI Rest		Period VII Rest	
	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation
J. D. T.	4.15	100	8.26	199	11.10	268	7.00	169	4.50	109	9.82	237	12.70	306	7.09	171	4.59	111
F. F-S.	3.06	100	8.25	270	9.53	311	5.05	165	3.28	107	9.52	311	9.99	326	5.49	180	3.46	147
L. L.	4.05	100	7.64	189	10.20	252	6.41	158	4.60	114	9.15	226	11.19	274	6.53	161	4.51	111
H. B.	4.01	100	7.84	196	8.25	206	5.98	149	4.56	114	11.80	294	12.30	307	8.04	200	5.12	128
F. W. P.	3.63	100	8.02	221	10.20	281	5.89	162	4.03	111	10.70	295	12.50	344	7.13	196	4.06	112
F. R. S.	3.94	100	9.35	237	10.90	277	6.48	164	4.47	113	11.70	297	18.50	470	12.10†	307	5.87	149
W. E.	4.85	100	8.29	171	11.20	231	6.97	144	4.77	98	9.67	199	13.80	285	8.25	170	4.78	99
I. C. S.	3.45	100	7.77	225	8.93	259	5.66	164	3.91	113	9.55	277	10.20	296	6.49	188	3.73	108
J. T. L.	3.85	100	8.89	231	10.30	268	6.31	164	4.36	114	12.20	317	14.80	384	8.18	213	4.68	122
H. R. M.	4.33	100	6.43	149	10.60	245	6.46	149	4.53	105	9.70	224	14.40	333	8.54	197	4.63	107
J. W.	3.63	100	7.94	219	7.51	207	5.24	144	4.15	114	10.60	292	9.84	271	6.82	188	4.37	120
Average	3.90	100	8.06	207	9.88	253	6.13	157	4.29	110	10.40	267	12.70	326	7.26‡	186	4.53	116
Cardiac Patients																		
M. McG.	4.87	100	9.26	190	13.20	271	8.80§	181	5.74	118	.....	...	.....	...	.....	...	.....	...
F. D.	6.12	100	11.10	181	12.60	206	9.84§	161	8.04	131	.....	...	.....	...	.....	...	.....	...
R. G.	6.16	100	12.00	195	12.30	200	10.20§	166	7.24¶	118	.....	...	.....	...	.....	...	.....	...
L. I.	4.39	100	9.64	220	11.40	260	7.72	176	5.41	123	.....	...	.....	...	.....	...	.....	...
F. C.	3.84	100	8.87	231	9.87	257	5.01	131	3.55	92	.....	...	.....	...	.....	...	.....	...
M. R.	5.88	100	10.10	172	13.40	228	10.50§	179	7.11	121	.....	...	.....	...	.....	...	.....	...
C. S.	6.15	100	11.90	194	12.80	208	7.83	127	5.17	84	.....	...	.....	...	.....	...	.....	...
B. O.	4.61	100	11.40	247	12.60	273	7.71	167	4.85	105	.....	...	.....	...	.....	...	.....	...
A. V.	5.03	100	9.65	192	11.70	233	8.07	160	5.42	108	.....	...	.....	...	.....	...	.....	...
E. W.	5.82	100	13.90	239	18.10	311	15.00§	258	8.57	147	.....	...	.....	...	.....	...	.....	...
F. K.	6.20	100	10.80	174	13.30	215	10.10	163	8.62**	139	.....	...	.....	...	.....	...	.....	...
Average	5.37	100	10.78	203	12.84	238	††	...	6.34	118	.....	...	.....	...	.....	...	.....	...

* First minute of rest after exercise.
† Two minute and 45 second period.
‡ Average does not include figures for F. R. S.
§ Four minute period.
¶ Four minute and 30 second period.
# Three minute and 30 second period.
** Four minute and 45 second period.
†† Average could not be calculated on account of variation in length of periods.

and IV. Determinations of minute-volume for shorter periods of time are, of course, less significant, but it is noteworthy that the pulmonary ventilation was greater for the first fifteen seconds of rest than for the last fifteen seconds of exercise in six normals and in five cardiac patients. The greatest subjective dyspnea thus corresponds closely with the highest minute-volume of pulmonary ventilation.

Immediately after the first minute of rest, in which the pulmonary ventilation reached its highest peak, there was a rapid recovery with a drop in the minute-volume from this maximum toward the level at which it was before the exercise was begun. There is a good deal of variation in the rate at which the minute-volume falls in different individuals, but in the normal subjects it generally reached to within about a liter of the original minute-volume during the fourth minute of rest. In the case of the patients with heart disease the decrease in the minute-volume after exercise was usually less rapid. This is best shown in the chart. It is impossible to determine just when the minute-volume of this group tended to return to what it was before the exercise, because in five instances the collection of air in Period III was not made in the fifth minute, but during the fourth minute the average minute-volume was two liters above the resting level. The cardiac patients thus took about one minute longer than the normals to return to approximately the same pulmonary ventilation that they had before the beginning of exercise. Even then, however, the return was less complete in the group of patients with heart disease than it was in the group of normals, for during Period IV seven of the former still had a minute-volume which was relatively higher than that of any of the normal subjects.

When walking upstairs with a pack (Period V) the normals began to experience a degree of dyspnea which was comparable to that observed in the cardiac patients in Period II. It is extremely interesting in this connection that the actual pulmonary ventilation per square meter surface area averaged almost exactly the same for the normals in Period V as for the patients with heart disease in Period II, although the increase over the ventilation at rest was proportionately much greater. In this second series of experiments the subjects again stated that dyspnea became more marked after they stopped their exercise. Period Va in Tables 6 and 7 gives the figures for the minute-volume during the first minute after the exercise. Just as in the case of the first walk (Period II), it was found that the minute-volume of air breathed was almost invariably greater in the first minute after exercise than it was during the exercise itself, and the most marked subjective dyspnea corresponded in time with the highest minute-voluume of pulmonary ventilation.

Rate of Respiration.—The observations on the rate of respiration in Table 8 show that it was distinctly higher in the patients with heart disease than in the normal subjects. This point was noticed only after the experiments on the normals had been completed, and there was no opportunity to obtain comparative observations on the rate of respiration at complete rest, but in eight cardiac patients pneumographic records were made after they had been lying on the bed absolutely quietly for at least one-half hour, and the rate was found to vary between 14 and 21 per minute. In all subjects a record of the rate of breathing was taken while they were sitting on a chair after having been at rest for at least one-half hour and before the mask was put on. The rate of respiration of the normals was between 12 and 20 per minute, and in eight subjects it was between 12 and 17, while in all the patients with heart disease it was between 17 and 26 per minute. The same difference holds with regard to the respiration rates while the subjects were standing at rest on the treadmill (Period I). In the group of normals the rate varied between 7.80 and 17.60 per minute, being below 15 in eight instances, while in the cardiac patients the rate was between 13 and 27.80 per minute, and was below 19 in only four instances. The fact that the rate of breathing was usually slower while standing in Period I than when sitting at rest resulted from wearing the face mask. During the walk upstairs (Period II) the rate of breathing increased in both groups, and the actual rate became considerably higher in the cardiac patients, but it is interesting that the average percentage increase over the average rate before exercise was almost exactly the same in the two groups. The fall in the rate of breathing, after the cessation of exercise, also appears to proceed in a similar manner in both sets of observations, and it was essentially complete in Period IV.

During the second exercise period (Period V), when the pack was carried, the rate of respiration of the normal subjects rose still further, reaching an average of 21.20 per minute, but this was followed by a rapid drop so that in Period VII the rate had returned to nearly what it was before the exercise.

Volume per Respiration.—Table 9 gives the average volume per respiration for each period in the two groups of subjects. This was obtained by dividing the total volume of air collected during the period by the rate of respiration. It is immediately apparent that the patients with heart disease breathed less deeply than the normal subjects when standing at rest (Period I). The average volume per respiration for the normals was 584 c.c. and for the cardiac patients it was 467 c.c., a difference of about 25 per cent. The variation was considerable in both groups, running from 412 to 870 c.c. among the normals, and from 320 to 683 c.c. among the patients with heart disease, but in eight of

TABLE 8.—Rate of Respiration.

Normal Subjects	Sitting at Rest	Period I Rest		Period II Exercise		Period III Rest		Period IV Rest		Period V Exercise with Load		Period VI Rest		Period VII Rest	
		Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation
J. D. T.	14.6	13.2	100	15.0	114	12.6	95	11.4	86	17.0	129	11.8	89	12.0	91
F. F-S.	15.4	14.0	100	20.0	143	16.2	116	14.0	100	22.0	157	16.4	117	14.0	100
L. L.	16.2	12.4	100	17.0	137	15.0	121	14.5	117	21.0	169	14.6	118	14.4	116
H. B.	21.8	16.0	100	25.0	156	16.0	100	14.6	91	28.0	175	20.6	129	18.4	115
F. W. P.	12.0	10.4	100	19.0	183	12.2	117	11.0	106	19.0	183	12.8	123	11.2	108
F. R. S.	16.8	17.6	100	20.0	114	22.6	128	16.4	93	30.0	170	23.6*	134	19.0	108
W. E.	20.0	17.4	100	20.0	115	19.6	113	18.6	107	18.0	103	19.2	110	18.0	103
I. C. S.	12.2	8.6	100	17.0	198	11.4	133	11.0	128	18.0	209	12.0	140	9.1	106
J. T. L.	14.2	7.8	100	11.0	141	11.6	149	9.2	118	26.0	334	16.8	215	12.6	161
H. R. M.	17.7	14.2	100	18.0	127	16.0	113	15.2	107	18.0	127	18.2	128	15.6	110
J. W.	11.8	10.0	100	15.0	150	13.0	130	12.8	128	16.0	160	13.6	136	12.6	126
Average	15.7	12.9	100	17.9	139	15.1	117	13.5	105	21.2	164	15.6†	121	14.3	111
Cardiac Patients															
M. McG.	19.4	17.2	100	24.0	140	19.8‡	115	19.6	114	....	...	....	...	....	...
F. D.	24.6	22.8	100	30.0	132	24.5‡	107	21.0	92	....	...	....	...	....	...
R. G.	20.4	23.8	100	26.0	108	21.5‡	90	21.2§	89	....	...	....	...	....	...
L. I.	18.6	17.0	100	27.0	159	21.6	127	20.2	119	....	...	....	...	....	...
F. C.	18.2	13.0	100	24.0	185	16.4	126	14.2	109	....	...	....	...	....	...
M. R.	24.2	22.0	100	28.0	127	28.2‡	128	27.4	125	....	...	....	...	....	...
C. S.	20.4	25.0	100	34.0	136	30.0	120	24.4	98	....	...	....	...	....	...
B. O.	24.8	20.4	100	36.0	176	28.2	138	22.6	111	....	...	....	...	....	...
A. V.	22.8	19.8	100	28.0	141	20.4	103	19.6	99	....	...	....	...	....	...
E. W.	17.2	13.0	100	23.0	177	23.2¶	178	19.0	146	....	...	....	...	....	...
F. K.	25.5	27.8	100	35.0	126	29.2	105	33.0#	119	....	...	....	...	....	...
Average	21.5	20.2	100	28.6	142	**	...	22.0	109	....	...	....	...	....	...

* Two minute and 45 second period.
† Average does not include figures for F. R. S.
‡ Four minute period.
§ Four minute and 30 second period.
¶ Three minute and 30 second period.
# Four minute and 45 second period.
** Average could not be calculated on account of variation in length of periods.

TABLE 9.—Volume Per Respiration.

Normal Subjects	Period I Rest		Period II Exercise		Period IIa *		Period III Rest		Period IV Rest		Period V Exercise with Load		Period Va *		Period VI Rest		Period VII Rest	
	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation
J. D. T.	630	100	1,108	176	1,820	289	1,115	177	794	126	1,157	184	2,320	368	1,202	191	768	122
F. F-S.	420	100	788	188	920	219	598	142	450	107	832	198	1,070	255	640	152	472	112
L. L.	613	100	846	138	1,120	*183	807	132	596	97	820	134	1,160	189	843	138	586	96
H. B.	469	100	588	125	970	207	700	149	584	124	790	168	980	209	728	155	520	111
F. W. P.	648	100	785	121	1,350	208	903	139	682	105	1,049	162	1,670	258	1,040	160	675	104
F. R. S.	412	100	860	209	830	201	527	128	500	121	713	173	1,040	252	940†	228	568	138
W. E.	501	100	745	149	1,060	212	643	128	461	92	968	193	1,380	275	775	155	473	94
I. C. S.	716	100	813	114	1,220	170	888	124	632	88	945	132	1,210	169	966	135	729	102
J. T. L.	870	100	1,429	164	1,340	154	958	110	835	96	828	95	1,190	137	856	98	653	75
H. R. M.	536	100	628	117	1,090	203	713	133	525	98	950	177	1,290	241	825	154	522	98
J. W.	613	100	892	146	980	160	680	111	548	89	1,120	183	1,110	181	850	139	585	95
Average	584	100	862	148	1,150	197	776	132	601	103	925	158	1,310	224	879‡	151	613	105
Cardiac Patients																		
M. McG.	500	100	764	137	1,090	195	880§	157	580	104	.....	...	.....	...	.....	...	.....	...
F. D.	510	100	702	137	850	167	760§	149	652	128	.....	...	.....	...	.....	...	.....	...
R. G.	488	100	865	177	1,050	215	893§	183	641¶	131	.....	...	.....	...	.....	...	.....	...
L. I.	470	100	652	139	990	211	648	138	487	104	.....	...	.....	...	.....	...	.....	...
F. C.	529	100	663	125	740	140	397	75	447	85	.....	...	.....	...	.....	...	.....	...
M. R.	447	100	605	135	840	188	635§	142	436	98	.....	...	.....	...	.....	...	.....	...
C. S.	387	100	550	142	540	140	410	106	332	86	.....	...	.....	...	.....	...	.....	...
B. O.	352	100	495	141	570	162	427	121	334	95	.....	...	.....	...	.....	...	.....	...
A. V.	391	100	534	137	770	197	598	153	425	109	.....	...	.....	...	.....	...	.....	...
E. W.	683	100	924	135	1,150	168	987#	144	680	100	.. ..	...	.....	...	.....	...	.....	...
F. K.	320	100	460	144	660	206	515	161	390**	122	.....	...	.....	...	.....	...	.....	...
Average	467	100	656	141	840	180	††	...	491	105	.....	...	.....	...	.....	...	.....	...

* First minute of rest after exercise.
† Two minute and 45 second period.
‡ Average does not include figures for F. R. S.
§ Four minute period.
¶ Four minute and 30 second period.
# Three minute and 30 second period.
** Four minute and 45 second period.
†† Average could not be calculated on account of variation in length of periods.

the normal subjects the volume per respiration was between 501 and 870 c.c., while in nine of the cardiac patients it was between 320 and 529 c.c. The difference in volume per respiration between the two groups depends, in part, on the fact that the normals were the larger men, but this does not completely explain it, for, when the volume per respiration was calculated with relation to the size of the subject, it was found that the average for the normal group was 317 c.c. per square meter of body surface area, and for the cardiac patients 274 c.c. per square meter. In eight of the normals the volume per respiration was between 278 and 483 c.c. per square meter of body surface area, and in ten of the cardiac patients it was between 215 and 283 c.c. per square meter.

In the period of exercise (Period II) the depth of respiration became greater in both groups of subjects. The actual volumes were considerably larger among the normals than among the cardiac patients, but, as was the case with the minute-volume and rate of respiration, the percentage increase of the volume per respiration over that before exercise was approximately the same in the two series of experiments. Immediately after the cessation of exercise, when the pulmonary ventilation was greatest (Period IIa), the depth of breathing increased in all the subjects, but the increase was proportionally more in the normal subjects than in the patients with heart disease. The actual tendency to more shallow breathing on the part of the cardiac patients was shown by the fact that at this period the volume per respiration was between 540 and 850 c.c. in seven of the eleven subjects, while in ten of the eleven normals it was more than 900 c.c

During the rest period after exercise (Period III), there was a rapid fall in the volume per respiration which proceeded at about the same rate in the two groups, and in the second rest period (Period IV) the depth of respiration in both groups was very nearly the same as it was before the exercise began.

In Period V, in which the normal subjects walked with the load, the volume per respiration was almost constantly a little greater than in the first exercise period, and it increased considerably in the first minute of rest after exercise (Period Va), but decreased again rapidly during the rest after exercise and was practically normal during Period VII.

An analysis of the factors of the pulmonary ventilation which have been studied shows that there is a fairly definite relationship between the rate of respiration and the minute-volume of respiration, in that there is a general tendency, to which there are individual exceptions, for the higher minute-volume to be associated with the more rapid rates of breathing. In a similar manner, the higher minute-volumes are usually accompanied by more shallow respirations. This general association between high minute-volume and rapid, shallow respiration is

probably explained by the fact that with shallow breathing the "dead space" of the upper respiratory tract becomes a more important factor since a relatively larger portion of each inspiration remains in it and takes no part in gaseous exchange. In order to maintain the necessary volume of alveolar ventilation it is, therefore, essential that the rate, and consequently the total minute-volume of respiration, shall be increased. There was no definite relationship between the volume per respiration and the vital capacity of the lungs in the patients with heart disease studied in these experiments. This is not at all surprising since the vital capacities were on the whole only slightly less than normal and the exercise was not severe enough to require deeper respiration than could easily be produced.

Heart Rate.—In an investigation of dyspnea in heart disease it would, of course, have been highly desirable to obtain information regarding the output of the heart, but owing to the lack of any suitable method it was necessary to limit the observations to determinations of the heart rate. In how far the heart rate and the minute-volume of cardiac output run parallel in such cases as are under consideration is a problem which cannot be settled definitely on the basis of our present knowledge, but the relation between the two is probably close enough to warrant a careful study of the cardiac rate. Since it is almost impossible to count the heart rate accurately by ordinary methods when subjects are walking on the treadmill, recourse was had to the electrocardiograph, which has the great advantage of enabling one to obtain continuous graphic records. By the use of two electrodes applied firmly to the sides of the body just below the axillae and a third electrode, which was grounded, placed just above the pubis, it was possible to obtain satisfactory records in almost every instance. Short electrocardiographic records were taken after the subject had been sitting quietly for one-half hour and again when he was standing on the treadmill (Period I). Twenty seconds before the exercise was begun a continuous electrocardiographic record was started which ran through the exercise period (Period II) and throughout the first minute after exercise. Frequent counts of the heart rate were made after this by watching the string of the electrocardiograph, and these counts were averaged to get the rate in each of the following minutes of the two rest periods (Periods III and IV). The same method was followed in Periods V, VI and VII. The results are shown in Table 10.

The heart rate was, in general, somewhat more rapid in the patients with heart disease than in the normal subjects. While sitting at rest the rates of the cardiac patients were between 86 and 102, while the rates of the normals were between 69 and 95, and in ten out of eleven subjects they were between 69 and 88 per minute. The same difference holds true for the heart rate while standing at rest on the treadmill

TABLE 10.—Heart Rate

Normal Subjects	Sitting	Period I *	Preliminary	Period II †				Period III ‡								Period IV *	Preliminary	Period V †				Period VI ‡								Period VII *
				15 sec.	30 sec.	45 sec.	60 sec.	15 sec.	30 sec.	45 sec.	60 sec.	2 min.	3 min.	4 min.	5 min.			15 sec.	30 sec.	45 sec.	60 sec.	15 sec.	30 sec.	45 sec.	60 sec.	2 min.	3 min.	4 min.	5 min.	
J. D. T.	73	76	76	88	98	102	110	98	95	78	80	71	72	69	69	74	76	96	108	108	116	114	109	90	86	80	69	67	69	73
F. F-S.	69	74	70	92	104	113	120	115	96	75	69	61	67	72	75	78	79	104	116	118	126	124	105	81	76	70	69	72	69	76
L. L.	88	88	88	104	112	112	116	108	103	97	80	98	78	90	82	85	84	108	116	120	124	120	104	104	84	88	78	78	72	81
H. B.	86	90	84	100	112	114	122	112	101	92	88	79	78	90	86	95	90	110	124	133	144	138	126	112	96	97	95	86	90	91
F. W. P. ...	76	87	86	96	105	110	110	111	108	93	90	86	90	86	95	92	98	102	115	127	126	123	114	104	99	89	86	95	90	92
F. R. S.	72	78	84	100	104	104	105	...	85	68	64	65	72	72	72	74	...	100	116	120	138	138	120	104	92?	75	66	60	64	77
E. W.	83	88	97	104	109	111	114	112	102	92	82	77	80?	84	90	87	91	102	116	120	128	124	116	103	91	83	78	80	90?	84
I. C. S.	77	81	...	...	...	...	...	...	...	...	...	...	67	...	...	80	...	...	...	...	...	...	...	...	...	...	78	82	86	82
J. T. L.	86	92	98	112	121	128	132	129	106	100	88	97	100	96	100	98	110	116	126	128	135	...	...	...	...	...	106	100	96	95
H. B. M. ...	80	84	...	99	110	115	116	116	112	97	88	79	77	78	82	85	91	108	120	124	132	139	126	123	108	94	78	72	78	82
J. W.	95	113	121	134	140	138	138	132	124	118	113	110	113	113	103	104	124	138	147	144	146	144	135	125	116	115	113	113	113	114
Cardiac Patients																														
M. McG. ...	87	...	98	112	123	128	133	136	128	120	112	84	82	90	98	101	...	...	...	...	...	...	...	...	...	...	...	...	...	...
F. D.	86	86	106	123	122	118	118	116	101	97	94	92	95	100	95	94	...	...	...	...	...	...	...	...	...	...	...	...	...	...
R. G.	97	112	102	115	125	130	133	140	136	125	110	106	111	113	113	110	...	...	...	...	...	...	...	...	...	...	...	...	...	...
L. I.	62	76	80	89	92	97	108	108	101	95	86	77	78	78	81	81	...	...	...	...	...	...	...	...	...	...	...	...	...	...
F. C.	82	96	...	112	126	128?	132	136	116	104	90	82	82	86	91	97	...	...	...	...	...	...	...	...	...	...	...	...	...	...
M. R.	90	90	...	100	109	115	120	119	108	104	94	88	86	82	90	93	...	...	...	...	...	...	...	...	...	...	...	...	...	...
C. S.	96	97	100	121	129	136	136	128	120	104	99	96	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
B. O.	68	82	83	104	114	119	120	106	88	80	75	70	64	72	72	71	...	...	...	...	...	...	...	...	...	...	...	...	...	...
A. V.	92	93	92	116	123	129	136	142	132	122	130	112	105	98	97	97	...	...	...	...	...	...	...	...	...	...	...	...	...	...
E. W.	99	105	...	108	124	136	144	148	148	148	148	146	134	129	127	119	...	...	...	...	...	...	...	...	...	...	...	...	...	...
F. K.	102	118	124	138	150	150	150	154	148	145	136	130	134	134	132	129	...	...	...	...	...	...	...	...	...	...	...	...	...	...

* Average rate for 5 minute period.
† Heart rates are given for each 15 seconds during exercise period of 1 minute.
‡ Heart rates are given for each 15 seconds for first minute, and then for each minute during remainder of period.

(Period I). Eight out of ten of the cardiac patients had rates between 86 and 118, and eight out of eleven normals had rates between 74 and 88 per minute. The average heart rate of the cardiac patients while standing at rest was 95 and that of the normal subjects was 86 per minute. The difference is thus about 11 per cent.

The column of figures under the heading "preliminary" in Table 10 gives the heart rate during the twenty seconds preceding the exercise period. The subject knew that he was about to start to walk and the changes in heart rate represent what is probably largely a nervous reaction. Among the normals there was an increase in rate of from five to nine beats per minute in four instances, a decrease of from one to three beats in three, and no change in two instances. In the group of cardiac patients seven showed a rise of from one to twenty beats, with an average increase of five, and three showed a fall of from one to ten beats, the average being four per minute. There is thus no constancy in the behavior of the subjects in this preliminary period and no distinct difference between the two groups.

At the onset of the exercise (Period II) there was an immediate rise in heart rate in both groups of subjects. In the normals the rate during the first fifteen seconds of exercise averaged 16 beats per minute higher than the rate while standing at rest, with variations of from nine to twenty-two among ten individuals. In the cardiac group the corresponding average increase was 17 beats, with variations of from three to thirty-seven in ten cases. During the last fifteen seconds of exercise, when the heart rate was usually greatest, the average increase of the normals was thirty-one, with extreme variations between twenty-three and forty-six, while the average increase in the group of cardiac patients was thirty-four, with extreme variations between twenty-one and forty-three per minute. The mean increase in heart rate was a little greater in the cardiac group than in the normals, as in seven out of ten cases of the former there was an increase of between thirty-two and forty-three, while in seven out of ten of the latter it was between twenty-one and thirty-two per minute. The differences are not striking, however, and the high heart rates reached by the patients with heart disease seem to depend largely on the fact that they started with a higher resting pulse rate.

Immediately after the cessation of exercise there was almost invariably a sudden drop in pulse rate in the normal subjects. This was such that even in the first fifteen seconds of the rest period (Period III) there was a fall of from two to twelve beats per minute from the rate at the end of exercise, with an average decrease of seven beats per minute in seven out of nine of the normal subjects. In one instance there was an increase of one beat per minute and in one instance there was no change in rate. The drop in pulse rate did not begin

so promptly in the cardiac patients, for in six out of eleven cases it rose slightly (between three and seven beats), in one it remained unchanged, and in only four was there a fall of between one and fourteen beats per minute in the first fifteen seconds of rest. The decrease in heart rate continued to be rapid in the normals so that between thirty and forty-five seconds after the exercise was stopped only four of the ten subjects had a pulse rate more than five beats per minute higher than it was before exercise was begun, and between forty-five and sixty seconds after cessation of exercise none had a heart rate more than five beats per minute above the rate standing at rest, and in six instances it was below this rate. This tendency to bradycardia continued so that during the second minute of rest the pulse was lower than it was before exercise in eight subjects. In the patients with heart disease the fall in heart rate went on more slowly. Between fifteen and thirty seconds after exercise was stopped the heart rate remained above what it was during exercise in two cases. Between thirty and forty-five seconds after exercise the heart rate was more than five beats per minute above that before exercise in all but one instance, and between forty-five and sixty seconds after exercise five of the ten cases still had a rate of more than five per minute above the rate while standing before exercise. Three out of nine patients with cardiac disease continued to have a heart rate considerably above that preceding exercise even during the second rest period (Period IV).

An analysis of the heart rate in these two groups of subjects does not allow of any satisfactory quantitative relation being established, but it is quite evident that the fall in heart rate in the normal subjects usually began immediately after exercise stopped and was constantly such that within one minute it had reached the level that it was before the exercise began, while in the group of patients with heart disease there was often a slight rise in rate after exercise stopped, followed by a slower fall to the level at which it was before exercise. During the rest period there was a tendency, in both groups of subjects, for the heart rate to pass through a phase in which it was even more slow than it was before the exercise.

In the period in which the normal subjects walked upstairs carrying a load on their backs there was again a rapid rise in pulse rate varying from ten to thirty-four beats per minute, with an average rise of twenty-one above the heart rate at rest in the first fifteen seconds of exercise. In the fourth fifteen seconds of exercise the increase of heart rate was from thirty-four to fifty-four, with an average rise of forty-two beats per minute. When the exercise was stopped there was an immediate slight fall in rate, averaging three beats per minute in the first fifteen seconds of rest in seven subjects, a rise of seven beats in one, and in one subject no change of rate. Between thirty and

forty-five seconds after the cessation of exercise all but one of the subjects continued to have a rate of more than five beats above the resting values, and between forty-five and sixty seconds after exercise the rate was more than five beats per minute above the rate before exercise in all but four subjects. In the second minute of rest the rate had come down at least to what it was before exercise in six out of nine instances, and in the third minute of rest this was the case in nine out of eleven subjects. There was a general tendency here also for the heart to assume temporarily a slower rate than before exercise. In general, therefore, this more severe exertion was followed by a rather gradual fall in heart rate in the normal subjects which resembled that observed in the patients with cardiac disease after moderate exercise.

DISCUSSION

In the previous sections a detailed analysis has been given of the changes produced by slight amounts of exercise in the metabolism, pulmonary ventilation, and heart rate in a group of normal young men and in a group of patients of approximately the same age with valvular heart disease. All of the latter were ambulatory patients, but the effect of the cardiac lesion varied in different cases so that while some of them suffered from dyspnea on moderate exertion, others were scarcely at all limited in their physical activities. In general, those subjects with the greatest tendency to dyspnea were those in whom the vital capacity of the lungs was lowest. Certain fundamental differences between the two groups were observed while they were standing at rest before the exercise began. In the patients with heart disease, the oxygen consumption, the heart rate, and the minute-volume of pulmonary ventilation were greater than in the normals, and the respiration was more rapid and more shallow than in the normal subjects. The metabolism of the group of cardiac patients, as measured by the oxygen consumption, averaged 12 per cent. higher than that of the group of normals, and, in the light of the fact that basal metabolism and heart rate have frequently been found to bear a close relation to one another, it is interesting to find that the average heart rate for the group of cardiac patients was about 11 per cent. above that of the group of normals. It seems probable that the more rapid heart action depended largely on the higher rate of metabolism. The minute-volume of pulmonary ventilation, on the other hand, averaged 37 per cent. greater in the group of cardiac patients than in the normals—an increase which is much too large to be accounted for entirely by the difference in metabolism. This high minute-volume of the respiration was associated with breathing which was more rapid and more shallow, and in which the percentage of oxygen taken out of the inspired air was less than in the case of the normal subjects. The higher minute-volume

breathed by the cardiac patients was probably the result of shallow breathing, with a consequent increase of the effect of the "dead space" of the upper respiratory tract. Under such circumstances the ventilation of the alveoli which is essential for proper gaseous exchange can only be obtained if the total amount of air breathed is increased, and this must be accomplished by raising the rate of respiration. Another possible explanation, however, deserves attention. It has been shown by Barr and Peters [7] that not only the total pulmonary ventilation, but also the effective minute-volume, is increased above normal in patients with cardiac decompensation. According to their observations this is due to the low percentage of carbon dioxid in the alveolar air of patients with cardiac decompensation and the consequent necessity of an increased effective ventilation in order to bring about the requisite elimination of carbon dioxid. Further studies on the blood by Peters and Barr [8] indicate that this low alveolar carbon dioxid is "largely brought about by an impairment of the efficiency of the pulmonary mechanism for the exchange of gases between the blood and the outside air" which "necessitates the maintenance of a greater difference in carbon dioxid pressure between the blood in the pulmonary circulation and the alveolar air to effect the normal carbon dioxid output." The cardiac patients who were the subjects of the present investigations, however, were all ambulatory, and one can hardly assume that they had a low alveolar carbon dioxid tension since Barr and Peters found this to be characteristic only of patients who were actually decompensated.

According to the calculations of Barr and Peters, the effective ventilation of a group of decompensated patients studied by Peabody, Wentworth and Barker [5] was about 30 per cent. greater than that of a similar group of compensated patients. Calculated on the same basis, with the assumption of a "dead space" for the subjects of 130 c.c. and an instrumental "dead space" of 50 c.c. additional, it is found that the average effective alveolar ventilation of the present group of normal subjects, while standing at rest (Period I), was 5,210 c.c., while that of the patients with heart disease, under the same circumstances, was 5,800 c.c. The difference, which is scarcely more than 10 per cent., can well be accounted for by the fact that the oxygen consumption of the group of cardiac patients was about 12 per cent. greater than that of the normals. Beyond this, therefore, the evidence indicates that in the two groups the effective, or alveolar ventilation, is of essentially the same magnitude and thus the findings of Barr and Peters do not account for the high minute-volumes observed in the compensated cases studied in this investigation.

7. Barr, D. P., and Peters, J. P., Jr.: Am. J. Physiol. **54**:345, 1920.
8. Peters, J. P., Jr., and Barr, D. P.: J. Biol. Chem. **45**:537, 1921.

The fact that cardiac patients have a greater total pulmonary ventilation while obtaining practically the same effective ventilation as normal subjects has an important bearing on the production of dyspnea, because it has been found that the sensation of dyspnea is closely associated with the breathing of a high minute-volume of air, and the explanation of this phenomenon should be sought. The question arises as to whether an essentially mechanical cause may underlie the tendency to a rapid and shallow respiration observed in patients with heart disease. In the group of patients under consideration the vital capacity was so little below normal that it is rather difficult to conceive of there being any restriction to the depth of breathing, especially while they were standing quietly at rest and using only a small portion of their vital capacity at each respiration. The possibility of some limitation to the depth of breathing is, nevertheless, worthy of consideration. Drinker, Peabody and Blumgart [9] have shown experimentally that engorgement of the pulmonary vessels may interfere with the entrance of air into the lungs, and their results indicate that the decrease in the vital capacity of the lungs in early cases of heart disease, in which there is no pulmonary edema or effusion into the pleural cavities, is due to congestion of the pulmonary circulation. Cardiac lesions potentially capable of causing engorgement of the pulmonary vessels were present in all the patients in the present study and in all but three the vital capacity was below the usual normal limits. The decrease was not great in any of the cases but it does not seem unreasonable to suppose that whereas the violent muscular effort exerted in measuring the vital capacity of the lungs would result in an essentially normal volume being taken into them, nevertheless, it might be easier for the same subject to take shallow respirations. If such were the case, they would instinctively breathe less deeply, even when they were at rest, than normal persons. Quite possibly this is a matter which concerns the Herring-Breuer reflex and there is much evidence to indicate the extreme sensitiveness of this mechanism. Even if such a conception is accepted it is not surprising to fail to find complete harmony in individual cases between the volume of the tidal air and the decrease of the vital capacity of the lungs. E. J. W., for instance, whose vital capacity was 62 per cent. of normal, breathed slowly and deeply while at rest and even during exercise. This may have been due to more or less conscious effort. Individual exceptions will always be found in the study of any mechanism which, like the respiration, is under the control of so many factors, chemical and nervous, and at present one can only suggest that the general tendency to shallow breathing seen in patients with heart disease is due to engorgement of the pulmonary circulation.

9. Drinker, C. K.; Peabody, F. W., and Blumgart, H.: J. Exper. M. (in press).

During the period of exercise, which consisted in walking sixty steps upstairs in one minute, there was an increase in oxygen consumption, heart rate, minute-volume, and rate and depth of respiration in the two groups of subjects, and the effect produced was essentially the same in both. A given amount of exercise apparently causes a rise in metabolism, heart rate and pulmonary ventilation in patients with cardiac disease that is proportionally the same as that observed in normal subjects. There was no difference in the type of reaction to exercise between the two groups.

The patients with heart disease became more short of breath as the result of the exercise than the normal subjects did, but in both groups the dyspnea was almost constantly described as being greater immediately after the exercise stopped than it was during the actual exercise itself. For this reason the first minute of rest after exercise was studied with particular care. It was found that the minute-volume of the respiration rose so that it was considerably higher during the first minute of rest than during the minute of actual exercise in both groups of subjects. The highest minute-volume of pulmonary ventilation was thus coincident with the greatest subjective dyspnea. The actual volumes breathed were greater in the case of the cardiac patients than in the case of the normals. The former, therefore, approached nearer to their maximum pulmonary ventilation and encroached farther on their pulmonary reserve.

Why is the sensation of dyspnea more noticeable after exercise than during exercise? It is reasonable to seek the answer to this question in the explanation of the high pulmonary ventilation after exercise, for the degree of dyspnea varies with the intensity of the stimulus to respiration, and the response of the respiratory center is indicated by the extent of the pulmonary ventilation. One of the most important stimuli to the respiratory center is carbon dioxid, and the respiratory quotients, which were generally low during exercise and high during the period following exercise, suggest that there was a lag in its excretion. This would result in a prolongation of its stimulation of the respiratory center, and cause a high pulmonary ventilation even after the exericse was stopped. The fact that the minute-volume of respiration was sometimes actually greater immediately after exercise than during exercise may depend in part on mechanical interference with the respiratory movements at a time when other bodily movements are being actively carried on.

Following the rise in the minute-volume of the respiration, which occurred immediately after exercise, there was a gradual decrease in minute-volume in both groups of subjects, but the return to the level which existed before exercise was distinctly slower in the patients with

heart disease than in the normal subjects. Hunt and Dufton[10] have recently called attention to the same phenomenon. It is undoubtedly due to an abnormal delay in the excretion of carbon dioxid or other stimuli of the respiratory center. The fact that the minute-volume increased during and after exercise in the same proportion in the cardiac patients as in the normals indicates that this lag is not due to the pulmonary ventilation being less efficient in the patients with heart disease. Further evidence of this is gained if the effective alveolar ventilation is calculated for the exercise period. Assuming again a total "dead space" of 180 c.c. the average effective ventilation of the normals was 11.6 liters and of the cardiac patients 13.2 liters per minute. The difference amounts to approximately 13 per cent. and is just about the same as the difference found during the rest period before exercise. There is, thus, no reason for considering that the prolonged increase of pulmonary ventilation after exercise in the patients with heart disease studied in this investigation was the result of inefficiency of the lungs in removing carbon dioxid from the system. The cause must be sought elsewhere and it is natural to consider the circulation.

The evidence to be derived from these investigations is incomplete because there were no direct determinations of the minute-volume of the circulation before and during exercise, but the observations on the heart rate bear on the question and are suggestive. In the group of normal subjects the heart rate dropped suddenly and rapidly immediately after the cessation of exercise, reaching the level at which it was before exercise in less than one minute. In contrast to this the decrease in heart rate after exercise in the patients with heart disease began later, was slower, and was sometimes preceded by a slight rise in rate just after the cessation of exercise. Martin and Gruber[11] believe that the sudden rise of heart rate at the onset of exercise is due to associated innervation and the passage of impulses from the cortex which inhibit vagus activity. The sudden fall in heart rate after exercise might be explained by the cessation of such depressing impulses but it is difficult to understand, on this basis alone, why the heart often remains rapid in the patients with cardiac disease. It may, perhaps, be accounted for by assuming the existence of some metabolic stimulus to cardiac acceleration which had failed to be eliminated with normal rapidity in these patients with impaired hearts. The rapid heart action would, then, represent an attempt to raise the minute-volume of the circulation, and this abnormal acceleration would constitute an indication of the inefficiency of the heart to meet the demands put upon it by the strain of exercise. It is, of course, in this sense that the same

10. Hunt, G. H., and Dufton, D.: Quart. J. Med. **13**:165, 1919.
11. Martin, E. G., and Gruber, C. M.: Am. J. Physiol. **32**:315, 1913.

phenomenon is commonly used as a clinical test. With an inadequate circulation the slow elimination of carbon dioxid is easily explained and its retention would result in a stimulation of the respiratory center and account for the prolonged increase of pulmonary ventilation.

According to the conceptions which have been outlined, therefore, the fact that the patients with heart disease had a greater subjective sensation of dyspnea after slight amounts of exercise than normal persons depends on two factors. They had a tendency to breathe less deeply than normal individuals, with the result that the total pulmonary ventilation was greater in order to obtain the same effective alveolar ventilation, and this large pulmonary ventilation was maintained for a longer period of time because the circulation became inadequate during the strain imposed by exercise and the elimination of carbon dioxid was delayed. In cases of heart disease which are more severe than those reported on here, and in whom the vital capacity of the lungs is markedly decreased, the mechanical interference with pulmonary ventilation, owing to inability to breathe deeply, plays a considerably greater rôle in the production of dyspnea.

The normal subjects did not become definitely short of breath as a result of walking upstairs and they were put through a second test, in which they took the same number of steps carrying a load on their backs in order that the development of dyspnea in them comparable in degree to that which occurred in the cardiac patients, might be studied. Greater changes were observed in the metabolism, heart rate and pulmonary ventilation, but the general type of change was the same as was present in the patients with heart disease who undertook less exercise. Even the slower fall in heart rate and minute-volume of respiration after cessation of exercise was seen. The most striking difference noted was that the tendency of the normals to breathe more deeply gave them more effective ventilation of the alveoli of the lungs and thus enabled them to meet a greater demand for oxygen with a lower total pulmonary ventilation. Thus, when walking upstairs and carrying a pack, the normal subjects had a considerably higher oxygen consumption than either they or the cardiac patients had when walking without the pack, but the average minute-volume of pulmonary ventilation was almost exactly the same for the normals when walking with the pack as for the cardiac patients when walking without the pack.

CONCLUSIONS

In a group of eleven ambulatory patients with heart disease it was found that the oxygen consumption and heart rate were slightly greater than in a similar group of normal subjects while standing at rest. Under the same conditions the minute-volume of the respiration was much greater in the cardiac patients and the breathing was more rapid and more shallow.

The slight amount of exercise involved in walking up sixty steps produced the same relative changes in oxygen consumption, pulmonary ventilation and heart rate in the two groups, but it caused more subjective dyspnea in the patients with heart disease. Exercise which was severe enough to cause a corresponding amount of dyspnea in normal subjects caused the same type of changes in oxygen consumption, pulmonary ventilation, and heart rate, but they were greater in degree. The response to exercise of patients with heart disease is qualitatively the same as that in normals, and their greater liability to dyspnea depends on a quantitative limitation.

Shortness of breath was most noticeable immediately after exercise was stopped, and at this time the pulmonary ventilation was largest. The return to normal of the minute-volume of the respiration and of the heart rate was delayed in the cardiac patients.

It is suggested that the two factors which account for the greater dyspnea in the cardiac patients are the inadequate circulation, which results in a delayed elimination of carbon dioxid, and the tendency to shallow breathing, which necessitates a relatively large pulmonary ventilation.

This investigation was begun in association with Dr. Howard F. West and Miss Edna H. Tompkins, and a large amount of preliminary work was done while they were in the laboratory. We regret that they were forced to leave Boston before the present series of experiments was begun, and wish to express our great appreciation of the assistance which they contributed.

STUDIES IN DIABETES INSIPIDUS, WATER BALANCE, AND WATER INTOXICATION

STUDY I

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Two years ago we developed a special interest in diabetes insipidus,[1] and as a result have been carrying out investigations on patients suffering from this disease. During the course of clinical studies certain observations were made which led to experiments in animals relative to water balance and to water intoxication.

In this study we shall report (1) the results of our clinical studies in the fifteen cases of diabetes insipidus observed during the last two years in the Mayo Clinic and in the University Hospital, Minneapolis; (2) the effects on urinary secretion of the subcutaneous injections of the extract of the posterior lobe of the pituitary gland in normal dogs and in dogs which have undergone resection of the renal nerves; and (3) the production of water intoxication by the administration of water by mouth subsequent to the subcutaneous administration of pituitary extract.

STUDIES IN DIABETES INSIPIDUS [2]

Etiology.—We have made an attempt to determine the etiology of the diabetes insipidus in our cases. One patient had brain tumor, not definitely localized but known to be supratentorial; another had a hypophyseal tumor, and four had syphilis; in nine cases no causative factor could be determined. The incidence of syphilis in our series is high. Its etiologic importance has been emphasized by Fournier,[3] Futcher,[4] and Oppenheim.[5] Whether or not syphilis was responsible for the diabetes insipidus in our cases could not be determined, but vigorous treatment for syphilis failed to exercise any significant effect on the course of the diabetes insipidus.

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1. Rowntree, L. G.: Diabetes Insipidus. In: Oxford Medicine, London, Oxford Univ. Press **4**:179, 1921.
2. The details of the clinical studies will appear in a separate publication by Dr. E. E. Larson.
3. Fournier: Quoted by Futcher.
4. Futcher, T. B.: Diabetes Insipidus. In: Osler, W., and McCrae, T.: Modern Medicine, Its Theory and Practice, Philadelphia, Lea & Febiger, 1914 **2**:721.
5. Oppenheim, H.: Die syphilitischen Erkrankungen des Gehirns, Specielle Pathologie und Therapie, Vienna, Nothnagel **9**:196, 1896.

The Nature of the Disturbance of Water Balance.—The cardinal symptoms of diabetes insipidus are related to disturbance of water metabolism; water is ingested and excreted in amounts far in excess of normal. In Trousseau's [6] case, for example, the most extreme on record, the fluid intake amounted to 40 liters and the urinary output to 43 liters a day. Thirst, the most annoying symptom, occasions extreme discomfort at times, while polyuria and polydypsia are the source of great inconvenience. Constipation and absence of sweating minimize the loss of fluid from the bowels and skin. The exact amount of fluid lost by way of the lungs and skin has not been determined accurately in diabetes insipidus so far as we know. Such studies are most desirable, but they necessitate the employment of special apparatus. Loss of fluid by way of the lungs plays a relatively smaller part than in the normal person. Studies of fluid balance in our cases show a striking correlation between the fluid intake and the urinary output. The literature abounds with similar results; but some writers have recorded urinary excretion somewhat in excess of the fluid ingested.

The fundamental question of whether the thirst or the polyuria is primary, we find difficult to answer. In this connection we have considered factors as follows: (1)the sequence of onset of symptoms, that is, whether thirst or polyuria constitutes the initial symptom; (2) the influences of various procedures in controlling thirst and urinary output; and (3) the presence or absence of organic or functional changes in the urinary tract.

Sequence of Symptoms.—By careful questioning with regard to the onset of the disease, it was possible, in three of our cases, to elicit a definite history of sudden onset of thirst, and to establish that in two thirst was primary, that is, it preceded the polyuria. In the first case the circumstances surrounding the onset of the disease were such as to make the evidence almost conclusive. The patient, a farmer's wife, was left alone in her home throughout the entire evening. She became extremely nervous and was frantic with fright. She lay in bed most of this time too frightened to move. During this period she developed a terrific thirst. She suffered no discomfort from bladder distention, nor did she void. She states that on the return of the family she rushed to the spigot and drank copiously of water, taking about two quarts. She insists that she did not void at this time, for in order to do so she would have been compelled to pass through several dark vacant rooms, which in her nervous state she would not have attempted. Polyuria developed on the following morning. The second patient, an intelligent man, insists that thirst was the primary symptom, and that it developed during the night. He got up and drank copiously of water,

6. Trousseau, A.: Lectures on Clinical Medicine, London, New Sydenham Soc. **3**:528, 1870.

voided but little, and did not suffer from any discomfort from bladder distention. In the third case both thirst and polyuria came on suddenly, but the patient was unable to recall the order of their appearance. In the remaining twelve cases the onset of the disease was insidious and consequently no conclusions could be reached concerning the priority of the symptoms.[7]

The Influence of Various Procedures in the Control of Thirst and Urinary Output.—Cannon[8] explains normal thirst on the basis of a local sensation resulting from local dryness of the buccal mucous membrane due to decreased secretion from the salivary glands, which in turn is dependent on the diminished supply of fluid furnished these glands by the body because of its depletion in water. Cannon further states that the osmotic pressure of the blood remains unchanged despite deprivation of fluids in the tissues. Dehydration of all tissues, including salivary glands, leads to diminished secretion of water by these glands. Normally the salivary glands furnish the index to the body need for water.

Thirst and a dry mouth were complained of by all our patients. Two volunteered the information that they experienced a peculiar sensation "as though the mouth were full of cotton." One demonstrated that "tenacious strings of saliva stretched from the roof of the mouth to the tongue, when the mouth was opened wide." There is little doubt that the viscidity of the saliva is increased.

We attempted to determine the rôle of the local sensation in the mouth with regard to water intake and urinary output in diabetes insipidus. We believe that specific local nervous influences have been excluded as a cause of the thirst since cocainization of the mucous membrane of the mouth and of the nasopharynx to the point of anesthesia failed to control either the polydypsia or the polyuria. In fact, in one case cocainization was pushed to the point of mild constitutional toxicity with no effect on the diabetes insipidus. In other cases pilocarpin was injected to procure salivary secretion, but without results. In four of these cases there was no evidence of decreased urinary output nor of diminution of thirst. As a result of these studies it appears that the thirst in diabetes insipidus is more than the mere expression of dryness of the oral mucous membrane.

The Presence or Absence of Organic and Functional Disturbances in the Urinary Tract.—Careful studies of renal function in diabetes

7. Since this paper was written Bailey and Bremer have reported their studies in experimentally induced diabetes insipidus before the Society of Endocrinology, Boston, June, 1921. They have demonstrated conclusively that thirst and polydipsia may precede polyuria.

8. Cannon, W. B.: The Physiological Basis of Thirst, Proc. Roy. Soc. London, s. B. **90**:283, 1918.

insipidus failed to incriminate any part of the urinary tract as an etiologic factor, and revealed no deviations from normal function, except in relation to water excretion and perhaps to salt excretion.

In all our cases the urinary output was markedly increased, from 3 to 14 liters a day. The specific gravity was markedly decreased, ranging, as a rule, between 1.001 and 1.004. Albumin appeared intermittently in small amounts in three cases, while demonstrable glycosuria was persistently absent. The excretion of phenolsulphonephthalein and the values for blood urea, creatinin, and uric acid were uniformly normal. Cystoscopic examination in two cases showed normal bladders. Ureteral catheterization revealed the fact that the increased secretion of urine was bilateral, and approximately proportional for both kidneys, and that the appearance time for phenolsulphonephthalein was normal from each side. Administration of pituitary extract with the ureteral catheters in place, reaching to the pelvis of the kidney, resulted in control of the polyuria and in a change in the concentration and color of the urine, within eight minutes in one case, and within ten minutes in another. These results conclusively exclude constriction of the ureter as a factor in the control exercised by pituitary extract on the polyuria and gross organic changes in the kidney and urinary tract. Hoppe-Seyler[9] presents the situation aptly when he says of renal function in diabetes insipidus, "it fails only by a little pituitrin of being normal."

The Results of Treatment.—The discovery by Schäfer[10] and his colleagues of the influence of the extract of the posterior lobe of the pituitary on the urinary output has created a new and growing interest in the subject of diabetes insipidus. Unfortunately, Schäfer's observations were made on anesthetized animals and led to the belief that the active substance of the posterior lobe possesses diuretic properties. Physiologists and clinicians were alike deceived with the result that diabetes insipidus was looked on by many as the result of overactivity of the posterior lobe. However, in 1913, von der Velden,[11] in Germany, and Farini and Ceccaroni,[12] in Italy, working independently, administered extract of the posterior lobe to patients suffering from diabetes insipidus and obtained an effect almost specific; thirst, polydypsia, and polyuria were all promptly and effectively controlled, at least for a temporary period.

9. Hoppe-Seyler, G.: Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandlung mit Hypophysenextrakt, München. med. Wchnschr. **62**:1633, 1915.

10. Schäfer, E. A., and Herring, P. T.: The action of Pituitary Extracts on the Kidney, Proc. Roy. Soc. London, s. B. **77**:571, 1905.

11. Von der Velden, R.: Die Nierenwirkung von Hypophysenextrakten beim Menschen, Berl. klin. Wchnschr. **1**:2083, 1913.

12. Farini, A., and Ceccaroni, B.: Influenza degli estratti ipofisari sull' eliminazione dell' acido ippurico, Gazz. d. osp. **34**:879, 1913.

DATA CONCERNING THE FIFTEEN CASES IN THE SERIES

The Effect of Pituitary Extract.—The effect of pituitary extract was studied in all our cases. Marked temporary results were obtained in all. The effects were immediate, and lasted for periods ranging from a few hours to four or five days (Figs. 1, 2 and 3). In mild cases the water balance was reduced to its normal level, while in more severe cases the level was reduced strikingly. Pituitary extract in gum acacia exercised as good an effect and resulted in a somewhat more prolonged control, although the local reaction was somewhat more severe. Effects of short duration sometimes follow the administration of pituitary extract by rectum.

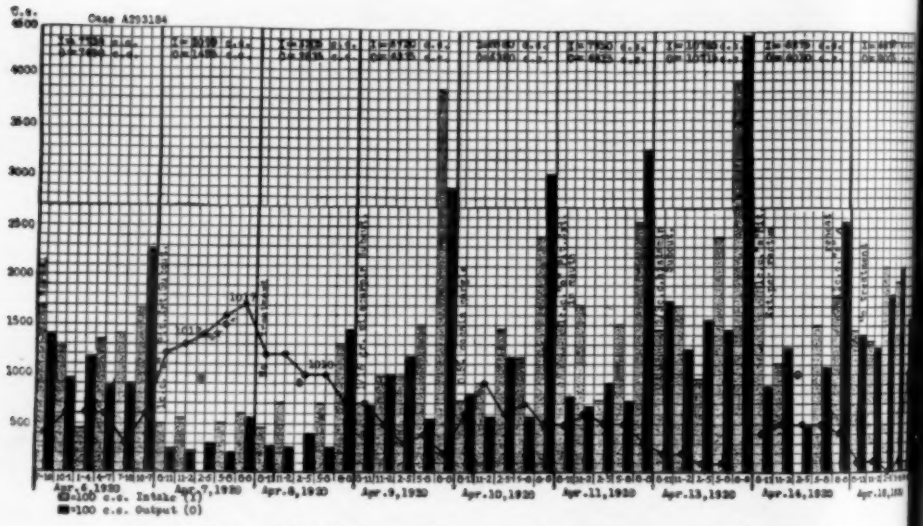

Fig. 1 (Case A 293,184).—Fluid intake, urine volume and specific gravity in the three-hour periods while the patient was receiving varying treatment.

With the decrease in the amount of urine the specific gravity rose to 1.010 or 1.025, and the color increased proportionately. With the readjustment of urine secretion the saliva flowed more freely; the skin became moist, and actual perspiration occurred in a large number of the cases. With the diminished desire for water the taste for it was frequently perverted, the patients referring to water at these times as being "stale" or "flat." A sensation of satiety and a feeling of fulness resulted from the intake of small quantities of water, for example, half a glass. This is in striking contrast to their usual experience. Prior to the administration of pituitary extract, a quart of water often failed to relieve the consuming thirst.

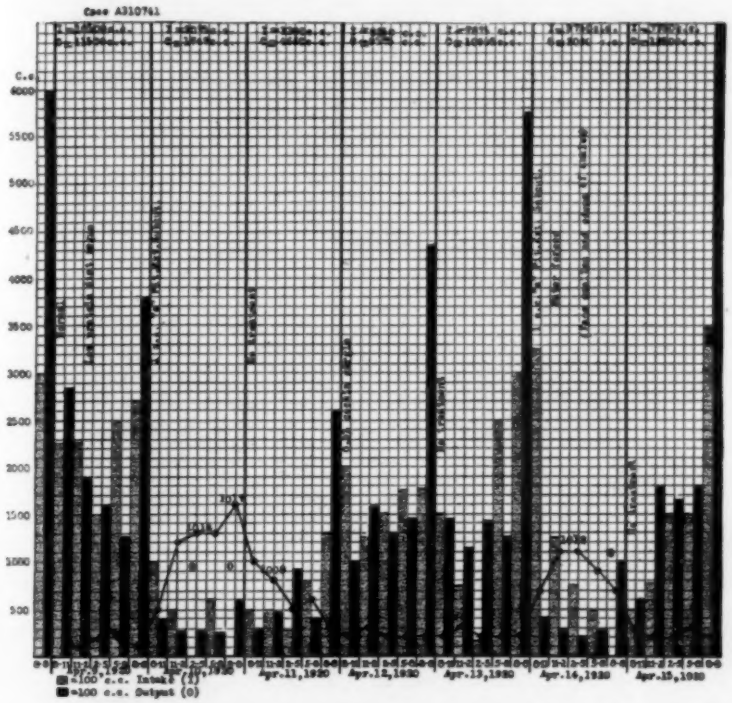

Fig. 2 (Case A 310,741).—Fluid intake, urine volume and specific gravity in three-hour periods during marked antidiuretic effect of pituitary extract and water intoxication.

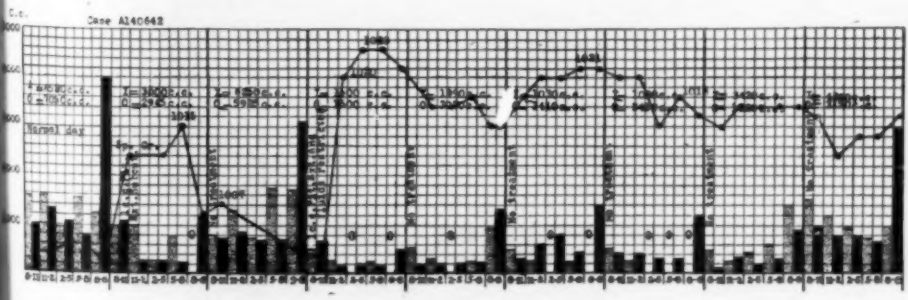

Fig. 3 (Case 140,642).—Prolonged antidiuretic effect of pituitary extract when patient exercised voluntary restriction on his thirst.

The volume of saliva secreted after the administration of pituitary extract increased definitely. This is illustrated in Figure 4 which contrasts the action of pituitary extract on the volume of urine and saliva of normal persons and of a patient with diabetes insipidus.

Effects of Histamin.—Histamin was administered subcutaneously in three cases. Constitutionally and locally its effect differed entirely from that of pituitary extract. In no instance was either the thirst or

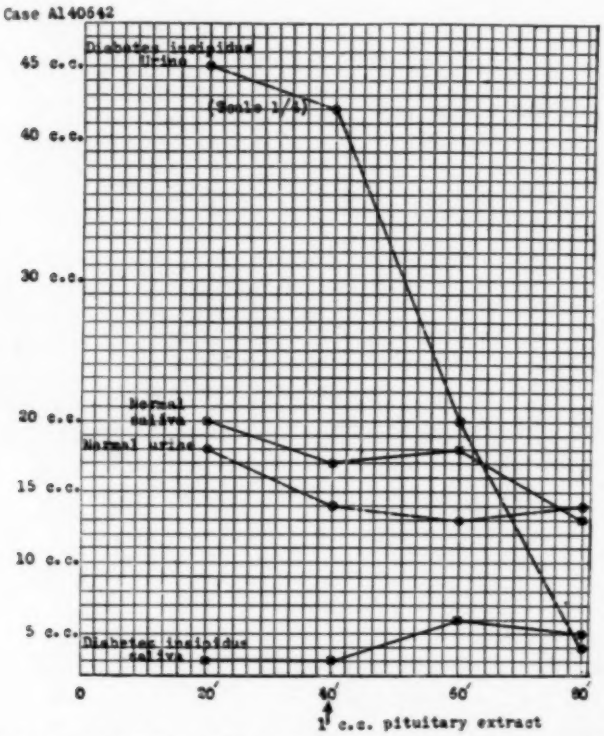

Fig. 4 (Case A 140,642).—Effect of pituitary extract on salivary and urinary secretion.

the polyuria decreased, except on one occasion when slight control was noted for three hours. The usual type of result may be seen in Figure 1.

Results of Spinal Puncture.—A spinal puncture with the withdrawal of from 5 to 10 c.c. cerebrospinal fluid was performed in six cases, without demonstrable effect on any of the cardinal symptoms. Because of the favorable reports in the literature we believed that the

amount of fluid withdrawn might be of significance. Consequently spinal drainage was done in three other cases, but in not a single instance was a favorable effect obtained.

Results of Treatment for Syphilis.—In the four cases with evidence of syphilis, treatment was carried out, but it has proved unavailing to date. Spinal puncture in three of these cases also failed to give relief.

The Effect of Restriction of Fluids.—Voluntary restriction of fluids was attempted in several of our cases, but it met with minor success in two only. One patient, a woman, succeeded in decreasing the intake from 5 to 6 liters a day to 1.5 liters, through her determined effort to refrain from water. Her case was unusual, however, the diabetes in all probability being hysterical in nature. In the second case early syphilis of the central nervous system complicated the diabetes insipidus. By the aid of 1 c.c. pituitary extract restriction to approximately normal amounts was obtained for a period of five days (Fig. 3). Without pituitary extract attempts at restriction accomplished but little, while pituitary extract alone failed to exercise control for periods longer than two days.

Before prescribing restriction of fluids the intense distress accompanying water fasting should be duly considered. One of our patients who had undergone a "restriction cure" at the hands of her local physician, had tears streaming down her face as she told us her story. In true diabetes insipidus little or nothing can be accomplished through restriction of the fluid intake, and the suffering inflicted is out of all proportion to the slight benefit obtained.

Metabolism.[13]—In a consideration of metabolism in diabetes insipidus the changes induced in normal persons by copious water drinking must be kept in mind, as has been pointed out by several authors. Rosenbloom and Price [14] give an excellent review of the literature on the metabolism in this disease. Gibson and Martin [15] have recently published results of metabolic studies before and after administration of pituitary extract.

Metabolism studies have been carried out in two cases of diabetes insipidus (Cases 140,642 and 330,908), the study in one being repeated during the patient's second visit to the clinic. Studies of blood chemistry were made in two other cases (Cases 317,545 and 323,015) before and after the administration of pituitary extract. The results in one case (Case A 330,908) are shown in Tables 1, 2 and 3. The water intake

13. The details of these metabolic studies will appear in a separate publication by Dr. J. F. Weir.

14. Rosenbloom, J., and Price, H. T.: A Metabolism Study of a Case of Diabetes Insipidus, Am. J. Dis. Child. **12**:53, 1916.

15. Gibson, R. B., and Martin, F. T.: The Administration of Pituitary Extract and Histamin in a Case of Diabetes Insipidus, Arch. Int. Med. **27**: 351, (March) 1921.

TABLE 1.—URINE ON METABOLIC EXPERIMENT (A 330908)

Day	Volume, C.c.	Specific Gravity	N/10 Acid, C.c.	Chlorin, Gm.	Total Nitrogen, Gm.	Urea Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinin Nitrogen, Gm.	Uric Acid, Nitrogen, Gm.	Urea Nitrogen, Per Cent. Total	Ammonia Nitrogen, Per Cent. Total	Creatinin Nitrogen, Per Cent. Total	Uric Acid, Per Cent. Total
Before treatment													
1	4,525	1.007	366	3.45	8.26	6.56	0.316	0.316	0.092	79.4	3.8	3.8	1.1
2	4,980	1.009	343	4.30	8.02	....	0.266	0.511	0.048	....	3.3	6.4	0.6
During treatment													
3	915	1.025	208	2.50	8.134	5.497	0.466*	0.493	0.071	67.5	5.7	6.1	0.9
4	1,200	1.024	356	3.40	8.20	7.092	0.300	0.537	0.120	86.5	2.5	6.5	1.5
After treatment													
5	4,445	1.018	318	7.19	9.27	7.998	0.309	0.501	0.116	86.4	3.2	5.4	1.2
6	5,960	1.006	419	5.721	8.02	6.385	0.308	0.475	0.117	79.6	3.81	5.9	1.5

* Urine voided, alkaline at one period on this day.

TABLE 2.—BALANCE OF WATER, NITROGEN AND CHLORIN (A 330908)

Day	Intake			Urine Output			Balance			Weight, Pounds
	Water, C.c.	Nitrogen, Gm.	Chlorin, Gm.	Water, C.c.	Nitrogen, Gm.	Chlorin, Gm.	Water, C.c.	Nitrogen, Gm.	Chlorin, Gm.	
1	5,189	8.42	5.94	4,525	8.26	3.45	+ 664	+0.16	+2.49	162.5
2	5,740	8.22	6.38	4,980	7.96	4.30	+ 760	+0.26	+2.08	162.5
3	3,193	7.78	5.44	915	8.14	2.50	+2,278	−0.36	+2.85	163.0
4	2,380	7.92	6.27	1,200	8.20	3.40	+1,180	−0.28	+2.87	164.7
5	4,732	8.61	5.62	4,445	9.27	7.19	+ 287	−0.66	+1.57	164.2
6	6,382	7.57	5.50	5,960	8.02	5.72	+4,422	−0.45	+0.06	162.0

TABLE 3.—BLOOD ON METABOLIC EXPERIMENT (A 330908)

Day	Hematocrit, Per Cent. Plasma	Degrees △	Plasma Mg. per 100 C.c.		Whole Blood Mg. per 100 C.c.					Remarks
			Total Nitrogen	Sodium Chloride	Total Nonprotein Nitrogen	Urea Nitrogen	Uric Acid	Creatinin	Sugar	
Before treatment										
1	67	0.515	1,171	648	29.8	14.9	2.68	1.90	128	Normal
2	68	0.530	1,142	658	26.5	14.9	....	....	108	Normal
During Treatment										
3	69	0.542	1,082	640	26.6	16.2	....	....	144	Pituitary extract
4	72	0.531	1,000	623	24.8	14.8	....	....	108	Pituitary extract
After treatment										
5	71	0.522	1,099	622	28.1	14.8	....	....	108	After period
6	69	0.546	1,129	648	27 0	13.2	....	....	112	After period

showed a marked fall in the three hourly and daily quantities after the administration of pituitary extract. The variations in the volume and specific gravity of the urine were marked and obvious. The positive water balance in the control period was small, harmonizing with the clinical observation of dry skin and mouth. There is marked retention of water after the first dose of pituitary extract, corresponding with the decreased urinary output. The patients generally report an increased excretion of urine in the period after treatment. In this case, however, the water intake kept pace with the increased excretion, but this fact, together with the increase in weight during treatment and the return to normal in the after period, indicates retention of water in the blood or tissues. The excretion of nitrogen varied but slightly

TABLE 4.—EFFECT OF PITUITARY EXTRACT IN NORMAL PERSON AND IN PATIENT WITH DIABETES INSIPIDUS CONTRASTED IN BLOOD PICTURE

			Plasma Mg. per 100 C.c.		Whole Blood Mg. per 100 C.c.					
Day	Hematocrit, Per Cent. Plasma	Degrees Δ	Total Nitrogen	Sodium Chlorid	Total Nonprotein Nitrogen	Urea Nitrogen	Uric Acid	Creatinin	Sugar	Remarks
					Normal					
1	65	0.523	880	600	42	....	....	....	...	Control
2	58	0.534	1,008	605	45	16	....	....	146	Control
3	60	0.533	977	610	40	15	....	....	152	Pituitary extract
4	61	0.534	942	618	37	13	....	....	149	Pituitary extract
					Diabetes Insipidus (A317543)					
1	61	0.522	1,058	629	....	5.0	2.4	1.3	...	Control
2	55	0.549	1,163	640	....	5.8	2.4	1.3	...	Control
3	67	0.511	940	607	....	6.6	2.4	1.3	...	Pituitary extract
4	67	0.513	970	597	....	6.1	2.3	1.3	...	Pituitary extract

throughout the experiment and the nitrogen balance showed no appreciable change. The chlorin excretion was decreased under treatment and chlorin retention was evident.

In the second case (Case 140,642), similar changes in the urine were noted, and more marked change in the water balance; there was a large negative balance as the effects of the drug wore off. There was a definite decrease in the excretion of nitrogen and an increased positive balance in the period of treatment. Chlorin also showed rather marked retention.

In the analysis of the blood in diabetes insipidus before and after administration of pituitary extract certain definite changes appeared. Typical results in one case (Case 317,545) are contrasted with those of a normal person (Table 4). The relative plasma volume is increased, and the molecular concentration, the total nitrogen, and the sodium chlorid of the blood are somewhat decreased, findings which might indicate a dilution of the blood. However, in the findings in the

experiments on metabolism there is evidence of a slight retention of nitrogen and chlorin, which does not appear in studies on the blood. Evidently water retention is the most prominent feature following administration of pituitray extract, and in all probability the effects on nitrogen and chlorin are secondary to water retention.

In all our experiments on metabolism and in all our cases of diabetes insipidus in which pituitary extract has been administered, there has been no diarrhea,[16] and an analysis of the feces in one case showed a normal quantity of water. There is no evidence that pituitary extract prevents the absorption of water from the gastro-intestinal tract of man, as has been claimed for it for rabbits by Rees.[17] Only small quantities of water have been found in the intestines and feces of our animals at necropsy.

Blood Volume.—Blood volume determinations by the vital red method were carried out in four of our patients, and in three of them before and after the administration of pituitary extract, that is, in the periods of high and low urinary excretion. The results obtained in the two earlier cases led us to believe that the blood volume, particularly the plasma volume, was increased in diabetes insipidus following the administration of pituitary extract, that the pituitary extract had specifically raised the renal threshold for water, and that the kidney failed to excrete water even in the presence of hydremic plethora in the blood. However, in one case no increase was found in either total blood volume or plasma volume, despite the completeness of control exercised by the pituitary extract on the polyuria. Prior to the administration of the drug the plasma and total blood volume were 3,460 and 4,805 c.c., respectively, and after the drug, 3,495 and 4,855 c.c., respectively. From these results it is evident that pituitary extract can cantrol the polyuria of diabetes insipidus and prevent polyuria following excessive ingestion of water without the development of any significant increase in blood or plasma volume. These findings are in keeping with the experimental results which we obtained in animals.

THE EFFECTS OF PITUITARY EXTRACT ON THE WATER BALANCE

Behavior and Rôle of Water in Metabolism.—In order better to understand the effect of the pituitary extract on the water balance, it is desirable to know more concerning the nature of water exchange in the body, the mechanism involved in its regulation, and the part played by the pituitary gland under normal and abnormal conditions. Water plays a fundamental part in metabolism, and is essential to the life

16. Diarrhea was present in animals suffering from water intoxication, but the amount lost by way of the bowels was relatively very small.

17. Rees, M. H.: The Influence of Pituitary Extracts on the Absorption of Water from the Small Intestine. Am. J. Physiol. **53**:43, 1920.

and function of every living cell. It is transported to and from the cells by the blood, provision for its exchange being made locally by the presence of lymph spaces and lymph channels. It constitutes 80 per cent. of the blood. Oxygen and food are also transported to the cells by the blood. Nature has arranged to supply the blood with water, oxygen, and food, according to the constancy of the need of the cells for each and in accordance with the complexity or simplicity of the mechanism involved in their metabolism. Water holds a position intermediate between oxygen and food, the continuation of its supply being less vital than that of oxygen and more than that of food. In

TABLE 5.—SUPPLY AND OUTPUT OF WATER

	Amount			Author	Remarks
Supply					
Water from drink and food	Average	Maximum	Minimum	Forster.....	Data collected in Munich; fluid includes 1 to 2 liters beer
	.....	3,500	2,300		
	2,290	2,440	820	Atwater and Benedict	Over a period of 49 days with subject in repose
	3,700	4,550	2,225		Over a period of 66 days with subject doing moderate work
Water from oxidation of Food	.....	480	240		On mixed diet of approximately 4,000 to 2,000 calories, respectively
	.. ..	.....	.....		
Output					
Urine.....	1,500	3,000	800	Emerson.....	So many factors effect the urinary output that only a general average is given here *
	2,000	.....	.....		
Skin.....	550	.....	.....	von Noorden	These are average figures for patient indoors on a medium diet of 1,800 to 2,000 calories. Total fluid lost by evaporation may reach 1,600 c.c. on diet of 3,500 calories and 3,250 c.c. on diet of 5,000 calories with patient doing moderate or heavy work. As much as 7.5 liters may be lost during excessive work
Lungs.....	400	.....	.....		
Fecest.....	60	300	60		On vegetarian diet with large stools the water content may reach 300 c.c. In diarrhea greater losses may occur
	to	.....	.....		
	300	.....	.....		

* In five cases followed by us during summer months, the output varied from 750 to 1,200 c.c. The figures for maximum and minimum simply indicate ordinary physiologic limits.
† Obviously this refers to normal loss in the stools.

health blood varies in volume and consistency within narrow limits only, possibly in order that the supply of these essentials to the cells may be kept almost constant. Fluctuations in physiologic needs, depending on variations in function are met largely by changes in the rate and volume of the blood flow to various organs.[18]

The source of the water of the body is found in the fluids taken by mouth in the form of food and drink and in the water which results from oxygenation of food within the organism. Water is excreted by the skin, lungs, kidneys, and bowels. The intake and output vary tremendously with the life, habitat, and habits of the individual. The

18. The intermediary water metabolism and the effects exercised by water ingestion are purposely omitted from discussion.

relative amount excreted through the various channels also varies extremely, reciprocal relationships playing a striking part at times, particularly with regard to sweat and urine. Although the variations are extreme, some idea concerning the normal relations in water balance, that is, in the intake of fluids and in the output of water by the various channels under differing conditions of diet and activity are presented in Table 5.

Effect of Extract of Posterior Lobe of the Pituitary Gland on the Urinary Excretion in Normal Men and Animals.—In order to ascertain the effects of pituitary extract on the urinary excretion of normal persons, five men were placed under careful observation. Urine was collected in three-hourly periods throughout the day, and as a single

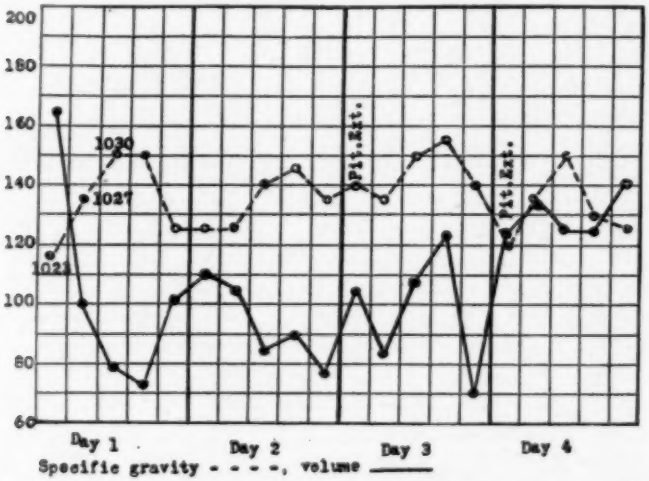

Fig. 5.—Average three-hour volume and specific gravity of the urine of five normal men before and after pituitary extract.

specimen at night. Diet and climatic conditions remained fairly constant during the period of observation, August, 1920. A two-day period of control preceded the administration of the drug, which was given at 8 a. m. on each day of the experiment. A composite curve in the urinary output and the specific gravity is shown in Figure 5. From these studies it is evident that the subcutaneous injection of 1 c.c. pituitary extract produced no appreciable effect on the urinary excretion, on the daily or three-hourly amounts, or on the specific gravity.

Other experiments were carried out on dogs; the water was given with pituitary extract and in some instances repeated at varying periods after the administration of the drug, in order to determine if diuresis

could be induced. Characteristic curves are reproduced in Figure 6. It is evident that diuresis can be readily induced by forcing the water intake after a single dose of 1 c.c. pituitary extract.

In Figure 7(a) is shown a composite curve of the results of a series of experiments in dogs, in which the urine was collected in half-hourly periods during the course of three hours. Each animal was studied under three conditions: (1) normal conditions, (2) after administration of water by mouth in amounts corresponding to 50 c.c. per kilo-

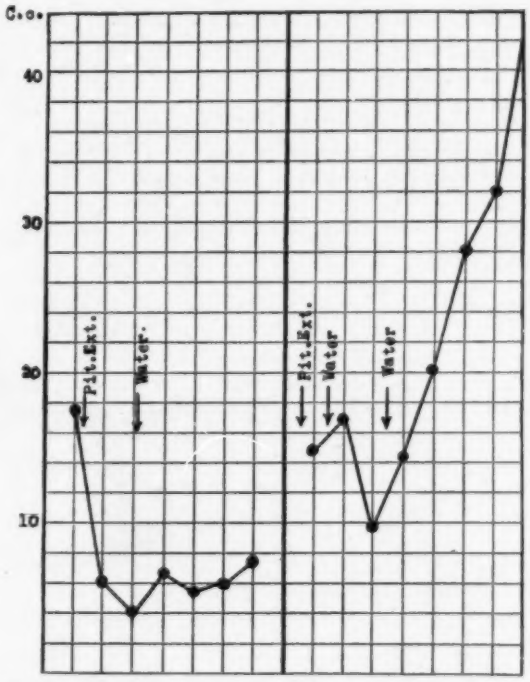

Fig. 6.—The antidiuretic effect of 1 c.c. pituitary extract in dogs can be overcome by repeated administration of water.

gram of body weight, and (3) after the simultaneous administration of pituitary extract, subcutaneously, and water by mouth in the amounts already indicated. These experiments demonstrate that the subcutaneous administration of pituitary extract definitely checks the production of water diuresis, although if the water is administered, urinary excretion is on a somewhat higher level than normal.

The next step was an attempt to localize the site and mode of action of the pituitary extract, that is, to ascertain the relation of pituitary

extract to the nervous control of renal function. The dogs of the first series were operated on and the splanchnic nerves to both kidneys sectioned.[19] A second series of experiments identical with those described was carried out (Fig. 7 [b]). A comparison of the total

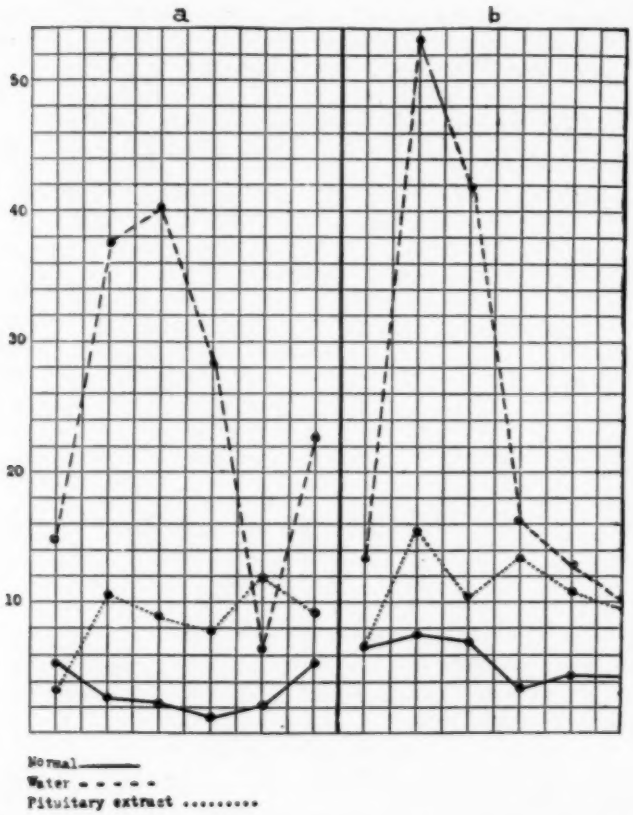

Fig. 7.—Average half-hour rate of secretion of urine in dogs under normal conditions, after water, and after water and pituitary extract (a) before section of the renal nerves (six dogs), and (b) after section of the renal nerves (four dogs).

results under these two conditions is shown in Figures 7 and 8. From these two series of experiments it is possible to deduce that (1) kidneys with nerves sectioned respond normally with a diuretic curve to

19. We wish to thank Dr. F. C. Mann and his associates for their kindness in performing the operative work on the animals used in these experiments.

water [20]; (2) this curve is largely abolished by pituitary extract, as in normal kidneys (the diuretic response after pituitary extract administration is on a slightly higher plane than under normal conditions), and (3) practically no change in the curve of the average half-hourly output under the three conditions of the experiment result from section of the renal nerves. It is evident, therefore, that the influence of pituitary extract in the prevention of diuresis is independent of the nerve supply of the kidney.

The Mechanism Involved in the Control of Diuresis by Pituitary Extract.—It is obvious from our clinical studies in diabetes insipidus and our experimental observations on the effect of pituitary extract in

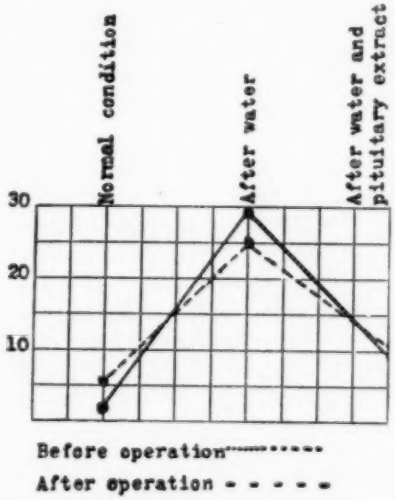

Fig. 8.—Curves showing average of secretion of urine in a series of dogs under normal conditions, after water, and after water and pituitary extract, before and after section of renal nerves.

the prevention of polyuria and our investigations of water intoxication that pituitary extract prevents polyuria. The mechanism of its action is difficult to explain.

Earlier in our work we were inclined to believe that pituitary extract raised the renal threshold for water and that a hydremic plethora resulted. However, in one case of diabetes insipidus and in several animal experiments, blood volume determinations failed to

20. Our results with the denervated kidney correspond to those already described by Marshall and Kolls.

Marshall, E. K., Jr., and Kolls, A. C.: Studies on the Nervous Control of the Kidney in Relation to Diuresis and Urinary Secretion, Am. J. Physiol. **49**:302, 1919.

indicate any increase of total blood or plasma volume. As a result of our failure to demonstrate hydremic plethora and increased renal threshold for water we are considering other possibilities.

In view of the results of our studies of blood chemistry and blood volume we are at present attempting to determine if it is possible that pituitary extract disturbs the relative ease with which the water of the blood leaves the blood stream to pass through the kidney to form urine, or to the tissues as body fluid. At present we are forced to admit our inability to explain the antidiuretic effect of pituitary extract. We are investigating the possibility of an abnormal escape of fluid from the circulating blood into the tissues.

INTOXICATION FOLLOWING THE ADMINISTRATION OF WATER BY MOUTH SUBSEQUENT TO GIVING EXTRACT OF THE POSTERIOR LOBE OF THE PITUITARY SUBCUTANEOUSLY

One of our patients at our solicitation continued, after the administration of pituitary extract, to take water in amounts to which he had become accusomed [21] and during a period of eight hours he ingested 5.25 liters, and excreted 800 c.c. of urine. In the course of three or four hours he became very ill, was nauseated and developed severe headache, and was forced to go to bed. Physical examination revealed only puffiness of the lower eyelids and slight edema of the ankles. Repetition of this experiment on the same and on another patient gave similar results, that is, nausea, vomiting, and headache, which forced the patient to go to bed. In one instance definite ataxia appeared.

On account of the severity of the reaction no further experiments were tried on patients, but similar studies were carried out on dogs. Water in large quantities was given by mouth subsequent to the administration of pituitary extract. This resulted in marked tremor, salivation, and at times vomiting. The symptoms were independent of the temperature of the water and were elicited with warm water as rapidly as with cold. On forcing the experiment convulsions and coma developed, and in one instance death supervened. As a result of these observations we undertook an investigation to determine the responsible factors, and studied separately the toxicity of water and of pituitary extract, and later the toxicity of water following the administration of pituitary extract.

Toxicity of Water.—In the classical experiments of Cohnheim and Lichtheim [22] in which they demonstrated the absence of anasarca,

21. The edema and toxicity resulting in this case were reported by one of us before the Society of Clinical Investigations, Atlantic City, 1920.

22. Cohnheim, J., and Lichtheim, L.: Ueber Hydrämie und hydrämisches Oedem, Arch. f. path. Anat. u. Physiol. **69**:106, 1877.

especially of edema of subcutaneous tissues when animals were given physiologic salt solution intravenously in large amounts (up to 90 per cent. of body weight) cramps were reported in a few instances. In an elaboration of this work by Magnus and Schäfer [23] no mention is made of these toxic manifestations.

Miller and Williams [24] recently published their results following the administration of large quantities of water to patients with chronic nephritis. They observed headache, dizziness, restlessness, chills, fulness of the abdomen, vomiting, dyspnea, and cramps in the legs, which were associated with marked increase in weight and definite elevation of blood pressure. In our experiments large amounts of water were given to dogs without the development of untoward signs or symptoms. One animal retained 2,500 c.c. during the course of seven hours and passed 1,500 c.c. urine without manifesting symptoms of intoxication. In another the administration of 3,500 c.c. resulted in salivation, vomiting, asthenia, and ataxia.

One of our colleagues, Dr. Amberg, has kindly furnished us with the following note, which is of interest in this connection. For the purpose of studying the influence of water ingestion on the elasticity of the skin as determined by the elastometer of Schade, two normal adults drank from 2 to 3 liters of water (not cold) within about fifteen or twenty minutes. For some time following the ingestion of the water no elastometric determinations could be made, on account of muscular twitchings. In the light of the experiments here reported it appears not impossible that this was the result of a slight water intoxication. There were no particularly uncomfortable subjective sensations.

Toxicity of Pituitary Extract.—Schäfer and Vincent [25] state that subcutaneous injections of pituitary extract to small mammals results in paralytic symptoms similar to those observed after suprarenal extracts. Cushny [26] states that large quantities can be injected without producing symptoms other than somnolence and muscular weakness.

23. Magnus, R.: Ueber die Enstehung der Hautödeme bei experimenteller hydrämischer Plethora, Arch. f. exper. Path. u. Pharmakol. **42**:250, 1899. Magnus, R., and Schäfer, E. A.: The Action of Pituitary Extracts on the Kidney, J. Physiol. **27**: Proc., ix, 1901.

24. Miller, J. L., and Williams, J. L.: The Effect on Blood-Pressure and the Nonprotein Nitrogen in the Blood of Excessive Fluid Intake, Am. J. M. Sc. **161**:327, 1921.

25. Schäfer, E. A., and Vincent, S.: The Physiological Effects of Extracts of the Pituitary Body, J. Physiol. **25**:87, 1899.

26. Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1910, p. 340.

According to Sollmann,[27] ataxia and motor symptoms, changes in carbohydrate metabolism, and emaciation develop after the excessive and long continued use of pituitary extract.

In order to determine the etiologic relationship of the extract of the posterior lobe of the pituitary to the symptoms observed in our studies some experiments were carried out; illustrative results appear in the following protocols:

PROTOCOLS OF EXPERIMENTS

PROTOCOL 1.—Dog 1, weight 9.8 kg. Pituitrin (Parke, Davis & Co.) subcutaneously.

Feb. 11, 1921.—Pulse 100, regular.

10:00 a. m.: 1 c.c. pituitary extract.
10:30 a. m.: 1 c.c. pituitary extract.
11:00 a. m.: 1 c.c. pituitary extract; diarrhea.
12:00 m.: 1 c.c. pituitary extract; diarrhea.
1:00 p. m.: 1 c.c. pituitary extract.
1:30 p. m.: 1 c.c. pituitary extract.
1:45 p. m.: Pulse 48, sinus arrhythmia, extrasystoles; bright and interested in other animals; no salivation; respiration 30.
2:25 p. m.: 1 c.c. pituitary extract.
3:15 p. m.: 1 c.c. pituitary extract. Pulse, 60; respiration, 40; appeared sick; lost "pep"; no interest in other animals; sleepy; no diarrhea or bladder frequency; no ataxia.
5:00 p. m.: 1 c.c. pituitary extract.
5:30 p. m.: 1 c.c. pituitary extract.
5:45 p. m. Animal more sleepy; no ataxia.

February 12: 10:00 a. m., pulse, 140, regular; animal active; appears normal. Intake from 6:00 p. m. to 10:00 a. m. 65 c.c.; output, 300 c.c.

PROTOCOL 2.—Dog 2, weight, 5.4 kg. Pituitary extract (Lilly Company) intravenously.

Feb. 16, 1921: Animal active; pulse, 80, regular.

2:25 p. m.: 3 c.c. pituitary extract; two minutes later inactive.
3:00 p. m.: "Sick"; at times seems unable to use hind limbs; lies flat on side.
3:05 p. m.: Heart rate, 44; sinus arrhythmia; restless.
3:07 p. m.: Defecation.
3:13 p. m.: 3 c.c. pituitary extract; lacks "pep"; diarrhea; pulse, 60; sinus arrhythmia.
3:29 p. m.: 3 c.c. pituitary extract; no resistance; slight tremor; appears weak.
3:31 p. m.: Vomited 15 c.c. yellow fluid, frothy.
3:40 p. m.: Pulse 62; reflexes active; vomiting again.
3:45 p. m.: 3 c.c. pituitary extract; several attacks of vomiting and bowel movements.
4:00 p. m.: 3 c.c. pituitary extract; feces and vomitus bile stained; mucus present.
4:15 p. m.: 3 c.c. pituitary extract; inactive; does not resist; pulse, 80.
4:40 p. m.: Greater activity.

February 17, 10:00 a. m.: Normal activity.

27. Sollmann, T.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, Philadelphia, W. B. Saunders Company, 1917, p. 344.

Toxicity of Water After the Administration of Pituitary Extract.[28]—Subsequently animals were given pituitary extract subcutaneously and large amounts of water through a stomach tube. Blood volume determinations and studies of the blood chemistry were made before the administration of pituitary extract, and again after the onset of the symptoms. The summary of the results is given in Table 6.

Early Manifestations of Toxicity.—The first symptoms noted may possibly be due to pituitary extract alone, namely asthenia, restlessness, frequent attempts at urination, diarrhea, and vomiting. Other symp-

TABLE 6.—Blood Volume in Water Intoxication

Dog	Weight, Kg.	Pituitary Extract, C.c.	Intake, C.c.	Output, C.c.	Hematocrit, Per Cent. Plasma	Total Plasma Volume, C.c.	Total Blood Volume, C.c.	Plasma per Kg.	Blood per Kg.	Total Nitrogen, Gm. per 100 C.c.	Sodium Chlorid, Mg. per 100 C.c.	Symptoms
E116	10.4	7 (4+3)	6,400 (4,000+ 2,400)	2,800 (1,500+ 1,300)	49 51	613 601	1,251 1,178	59 58	120 113	0.763 0.743	480 430	Drowsiness, salivation, restlessness. Frequent attempts at urination. vomiting, ataxia, convulsions, coma
E291	7.4	3	1,500	500	46 46	370 389	794 840	50 53	107 114	....	... ...	Drowsiness, salivation, tremor, ataxia, vomiting, convulsions, coma, involuntary evacuations of bowels and bladder
E290	9.0	5	5,000	2,000	53 57	618 526	1,157 923	69 58	128 102	0.490 0.595	460 390	Preoperative: Marked frequent attempts at urination; diarrhea, drowsiness, restlessness, ataxia, tremor, twitchings, salivation, convulsions, coma
E290	8.5	3	3,150	2,225	55 57	570 650	1,036 1,140	67 76	122 134	....	... ...	Postoperative Same symptoms

toms, tremor and salivation, next appear, possibly due to water alone. These develop usually after approximately 300 c.c. of water has been given per kilogram of body weight as a minimum. This stage continues for a variable period when another set of symptoms develops. The animal becomes very drowsy, and later shows muscular twitchings and ataxia on standing or walking. This may be designated as the preconvulsive stage. In spite of mental dullness the animal evidences hypersensitiveness to external stimuli, such as result from picking up the stomach tube or passing it. Such procedures may precipitate the convulsive stage.

28. Water introduced intravenously as physiologic solution of sodium chlorid results in an entirely different set of phenomena, the dogs dying with edema of the lungs.

Later Manifestations of Toxicity; Convulsions, and Coma.—Convulsions were characteristically epileptiform in type; first a tonic stage, followed immediately by a clonic stage. During the tonic phase the head retracted, the jaws set, respiration ceased, and the animal became cyanosed. Then sudden and violent clonic spasms developed, accompanied by frothing at the mouth and involuntary bowel and bladder evacuations. During the convulsive stage the pupils were markedly dilated, contraction occurring immediately after the cessation of the clonic spasms. During or following the convulsive stage the dog usually showed running, swimming, or snapping movements and at times barked and growled, as though participating in a fight. Coma or somnolence persisted for a longer or shorter period, but the animal usually recovered fully during the course of the next few hours. Passage of the stomach tube and the administration of more water brought on further convulsions, which, if continued, ended in death. Vomiting and salivation occurred usually after the administration of from 200 to 300 c.c. water per kilogram of body weight. Occasionally an animal failed to manifest salivation. Some animals made frequent attempts to urinate while others apparently exhibited no evidence of bladder irritability.

Several animals in which double renal nerve section had been performed were given pituitary extract and water. The same toxic symptoms developed but no increase or decrease in the facility with which they could be produced was noted. This further indicates that the antidiuretic action of pituitary extract is independent of the nerve supply of the kidney. A protocol of one of these experiments is presented below:

PROTOCOL 3.—Dog E 249, weight, 11.4 kg.[29] Water by mouth subsequent to pituitary extract subcutaneously.

Feb. 7, 1921.—11:50 a. m.: 1 c.c. pituitary extract and 500 c.c. water.

1:45 p. m.: 1 c.c. pituitary extract and 500 c.c. water.

2:45 p. m.: 1 c.c. pituitary extract and 500 c.c. water; some frequency of micturition.

3:15 p. m.: Has vomited 1,000 c.c.

3:25 p. m.: Animal found in cage, unconscious, frothing at mouth, head retracted; jerking of jaw and leg muscles. On being taken from cage, was unable to walk, lay on side and went through running movements, jaws still snapping. Prostration marked, movements easily restricted; semiconscious.

3:40 p. m.: Involuntary bowel evacuation, liquid. Running movements stopped; attempts to walk unsuccessful.

3:45 p. m.: Conscious, but lies quiet; unable to attract animal's attention; few attempts at walking movements; respiration, 70; muscles rather flaccid.

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29. Other experiments are in progress which involve more careful consideration of the weight of the animal. To date increases in weight greater than 1 kg. have not been encountered.

3:57 p. m.: Pulse, 100; pupils small; twitching muscles; feet lie as if asleep; eyes open; listless; few attempts to get up; respiration, 32.
3:59 p. m.: Gets up, walks in circular course, lies down.
4:02 p. m.: Diarrhea, hardly able to stand up, does not respond to call, is not frightened.
4:06 p. m.: Various attempts to rise.
4:08 p. m.: Walks, seems blind, bumps into objects.
4:15 p. m.: Walks again, bumps into objects; weight, 11.6 kg.
4:18 p. m.: Walks until exhausted; defecation.
4:25 p. m.: Improving; vision returning; attention can be attracted slightly.
4:27 p. m.: Pulse 108, deep respiration; frequent urinations, little or no urine.
4:45 p. m.: 500 c.c. water; very restless, running.
4:48 p. m.: Defecation.
4:50 p. m.: Running less rapidly, slightly ataxic, salivated.
4:52 p. m.: Running less rapidly, walks some, more ataxia, lists to left.
4:55 p. m.: Complete ataxia, unable to stand.
4:56 p. m.: Convulsion, head retracted; tonic and clonic phases, running movements; vomited; salivated.
5:03 p. m.: Convulsion.
5:04 p. m.: Convulsion.
5:12 p. m.: Convulsive movements.
5:20 p. m.: Has been in continuous convulsions, unconscious, continuous snapping movements of jaws, pupils widely dilated.
5:30 p. m.: Same condition, more convulsions, pupils contracted after convulsion, dilated during convulsion.
5:45 p. m.: Died in convulsion.

Necropsy revealed early onset of rigor mortis, normal chest and lungs, and slight congestion of the liver and kidneys. The stomach contained about 65 c.c. fluid and the intestine about 25 c.c. No free fluid was found in the pleural or peritoneal cavities, and there was no evidence of edema of the subcutaneous tissues of the neck or of the extremities. The brain, on removal, appeared to be normal in every respect.

Thus we have definite evidence of toxic symptoms produced by water, when the water-secreting function of the kidney is diminished through the subcutaneous administration of 3 c.c. pituitary extract.

While the experiments were in progress an attempt was made to determine the mechanism of production of the convulsions. Kymographic records were procured in some of these experiments. A typical tracing is presented (Fig. 9). Hydremic plethora as a cause was first considered, but no increase in the total blood or plasma volume by the vital red method, nor any constant increase in relative plasma volume by the hematocrit could be demonstrated (Table 6).

The total nitrogen and the sodium chlorid content of the plasma showed usually a slight decrease after the onset of symptoms. The urine volume during the following twelve hours was always increased, usually to about 500 c.c., indicating a rather rapid excretion of the retained fluids. Clinical evidence of edema was absent in all the animals studied.

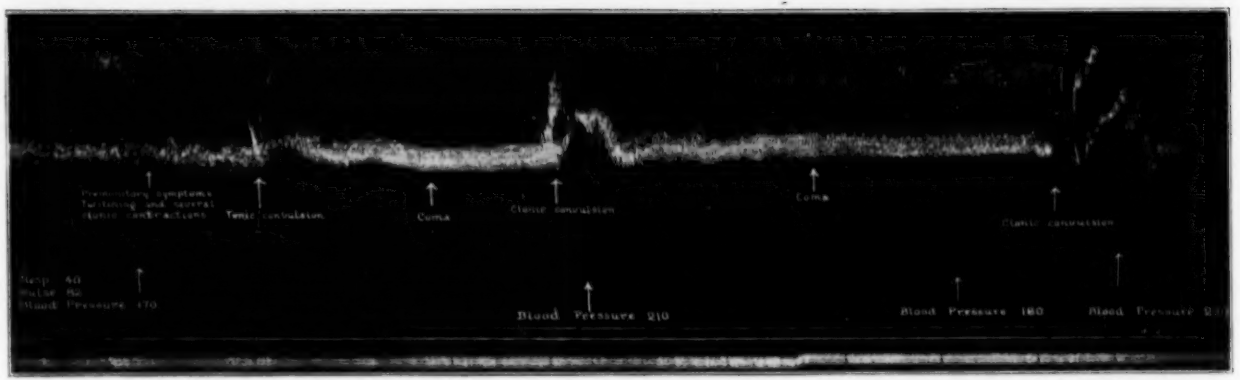

Fig. 9.—Water intoxication. Respiration, pulse and blood pressure during convulsions in a dog.

The Cause and Significance of Convulsions and Coma.—The immediate cause and the mechanism of production of these phenomena have not been determined. But it has been demonstrated that neither pituitary extract nor water alone [30] in similar, or even larger amounts, is capable of producing them. Edema of the brain, suggests itself as a logical explanation, but we have not succeeded in proving this to our own satisfaction. Table 6 presents the plasma and blood volume values as determined before and after water intoxication. From this it is apparent that increased blood volume has been excluded in at least some of our experiments. A marked increase in blood pressure is encountered in water intoxication. The rise is tardy in onset and

TABLE 7.—BLOOD PRESSURE CHANGES IN WATER INTOXICATION

Time	Water, C.c.	Weight, Kg.	Pitultrin, C.c.	Blood Pressure	Pulse	Respiration
11:00 a. m.	...	13.6	.....	140	84	..
11:20 a. m.	...	13.6	1 "0" Subcutaneously	140	..	..
11:30 a. m.	700	14.3	.....	140	..	..
11:45 a. m.	450	14.6	.....	160	..	..
11:50 a. m.	...	14.6	1 "0" Subcutaneously	150	72	22
12:00 m.	1,000	15.6	.....	140	..	..
1:00 p. m.	...	15.6	1 Subcutaneously	140	..	..
1:15 p. m.	1,000	16.4	.....	140	..	..
2:05 p. m.	500	16.9	1 Subcutaneously	150	70	24
3:05 p. m.	...	16.8	1 Subcutaneously	170	..	..
3:10 p. m.	500	17.2	.....	180	..	..
3:30 p. m.	...	0	1 Intravenously	190	..	..
4:00 p. m.	1,000	18.1	.....	206	72	26
4:30 p. m.	...	18.1	.....	...	..	..
4:40 p. m.	...	18.1	1 Intravenously	200	82	20
4:50 p. m.	...	18.1	.....	140	22	..

gradual in development and may reach a comparatively high level (Table 7; Fig. 9). However, the changes in blood pressure do not appear to be striking enough to account for the toxic manifestations.

Nausea, vomiting, muscle twitching, spasms, asthenia, convulsions, and coma developing in the presence of an obvious derangement of water excretion strongly suggest uremia, especially when death supervenes. But in the absence of increased values for blood urea, and in view of the rapidity of their appearance and disappearance, it does not seem at all probable. However, it is of more than passing interest to learn that the entire series of symptoms so frequently found in uremia can result from a common cause. From the standpoint of sudden onset and recovery eclampsia is also suggested.

30. Since this paper was submitted for publication, further experiments have been carried out and convulsions have been produced with water alone. The results of these further studies will be published later.

Convulsions of sudden onset characterized by a tonic and a clonic phase, associated with involuntary evacuations, and frothing at the mouth, followed by coma, and ending in complete recovery suggest epilepsy. On the other hand, nausea, vomiting, asthenia, and ataxia characterizing the earlier period of development of these phenomena have no resemblance to epilepsy. The possibility of reflex factors from the gastro-intestinal tract at least must be considered, since strangury and retching constitute marked features at times. A condition resembling status epilepticus and ending in death has also been observed.

In the absence of definite information relative to the seat, origin, and mechanism of production of these phenomena speculation is futile; it would be wiser perhaps to leave all such questions to the future.

CIRCULATORY COMPENSATION FOR DEFICIENT OXYGEN CARRYING CAPACITY OF THE BLOOD IN SEVERE ANEMIAS*

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It is a well known fact that persons suffering from severe chronic anemias do not show the signs of anoxemia when at rest even when the oxygen carrying capacity of each cubic centimeter of blood is below the normal venous unsaturation, or, in other words, when the oxygen content of each cubic centimeter of arterial blood is less than the average amount of oxygen normally abstracted from the blood by the tissues during its passage through them. We recently studied a case of pernicious anemia in this hospital in which with a hemoglobin of 12 per cent.[1] and an oxygen carrying capacity of only 2.2 c. c. per hundred cubic centimeters of blood there was no dyspnea, no acidosis, no increased pulse rate and a normal basal metabolism or rate of oxygen consumption. As it has been frequently shown that the normal resting human organism abstracts an average of 5.5 c.c. oxygen from the blood in the capillaries, it was necessary to explain how anoxemia was avoided in this case, with normal basal metabolism or oxygen consumption, and an oxygen content per cubic centimeter of arterial blood less than half the amount normally abstracted in the capillaries for the processes of oxidation.

The explanation of this condition in our case contains the solution of the problem of the compensatory mechanism in severe anemias, and we feel that it is of sufficient interest to justify publication, especially as it emphasizes the necessity for bed rest in severe anemias and introduces a method of minute volume determination on man which may be of value in cardiovascular investigation.[2]

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1. All hemoglobin determinations were done by the method of Palmer.[3] In this method a standard blood is saturated with oxygen and its oxygen capacity determined. An oxygen capacity of 18.5 c.c. per hundred cubic centimeters blood is given a hemoglobin value of 100 per cent. Having determined the oxygen capacity and hemoglobin value for the standard blood, this blood is now colorimetrically compared to the patient's blood by means of the Haldane carbon dioxid method. In this way the percentage of hemoglobin always has a definite relation to oxygen carrying capacity and the values of different observers working in different clinics are based on the same 100 per cent. standard.

2. J. Biol. Chem. **33**:119, 1918.

3. This method was first suggested by Fick, Ges. Werke **3**:573.

REPORT OF CASE

History.—A male, aged 49, entered the hospital complaining of pain in epigastrium and weakness, progressively increasing during past five years. He had a sore mouth two years ago. The skin had been yellow for years. He now complains of paresthesia in the legs.

Examination.—Lemon colored skin, with large pigment patches over neck and lower arms; no emaciation; petechiae on various parts of the body; mucous membranes pale; tongue smooth. Lungs normal. Heart apparently not enlarged to percussion. Systolic murmur present, loudest just inside apex. Systolic murmur at base is transmitted into carotids. Venous hum over jugulars. Spleen just at rib margin, moves 2 cm. below on deep inspiration. Tendon reflexes exaggerated, vibratory sense lost in legs. Sense of position questionable in legs.

Blood Findings on Entrance.—Red Cells, 1,600,000; hemoglobin, 42; index, 1.3; white cells, 3,600. Smears show many poikylocytes, anisocytosis, polychromatophilia and stippling, many megalocytes; no normoblasts, polymorphonuclears, 62 per cent.; lymphocytes, 33 per cent. No platelet count was made on entrance, later on when the hemoglobin had fallen to 12 per cent. the platelet count was 22,000; 4 per cent. reticulates. Normoblasts and megaloblasts were seen frequently in later smears.

Stomach Content After Boas Meal.—No "free acid" and a total acidity of 1 per cent.

Fragility test showed beginning hemolysis at 0.5 per cent. and complete at 0.35 per cent. The daily average of output of urobilin was 25,000 units.

Despite transfusions and regulation treatment, the patient's condition gradually became worse, and eight months after entrance the patient died with a hemoglobin content of only 8 per cent. Throughout a period of two months the hemoglobin content was 12 per cent. and the red count was about 550,000. It was during this period that the laboratory data were obtained. The necropsy confirmed the diagnosis of pernicious anemia.

Necropsy revealed a dilated heart with moderate increase in the thickness of ventricular musculature. Microscopic sections of heart muscle showed both hypertrophic and atrophic fiber. In certain areas there was vacuolization of this fiber. There was every evidence that death was due to circulatory failure. There was about one liter of transudate in each thoracic cavity. There was passive congestion of liver and spleen. The pathologist said that death was due to failure of the circulation.

April 3, 1921, two basal metabolism determinations were done with the Benedict unit apparatus and were found to be 1,454 calories, or 4 per cent., higher than the average normal value as predicted according to DuBois [4] and 15 per cent. higher than the basal metabolism as predicted according to Benedict.[5] Certainly the basal metabolism was not slowed up in this case. A few days later basal metabolism determinations were repeated and gave 1,451 calories. The oxygen

4. DuBois, D., and DuBois, E. F.: Arch. Int. Med. **17**:863 (July) 1916.
5. Benedict and Harris: Biometric Study of Basal Metabolism in Man, 1919.

consumption as determined by the apparatus was 213.5 c.c. per minute. If now we can find the oxygen abstracted from each cubic centimeter of blood leaving the lungs and passing through the peripheral circulation back into the right heart we can very easily calculate the number of cubic centimeters of blood passing through the lungs per minute or the number of cubic centimeters of blood leaving each chamber of the heart per minute. It is thus necessary to know the oxygen content of the arterial blood and the oxygen content of the venous blood. The oxygen content of the arterial blood is given by the hemoglobin determination according to the Palmer method. It is true the Palmer method gives the maximum oxygen content of the blood at atmospheric pressure of oxygen but this value has been shown by experiment to be only 5 per cent. above the value for arterial blood as actually determined. The Palmer determination on this blood, April 2, gave hemoglobin 12.2 per cent. The total combined and dissolved oxygen was 2.4 c. c. per hundred c. c. of blood. The determination of the mean oxygen content of the venous blood contains a slight error. We took the blood from the arm vein and determined its oxygen content according to the Van Slyke method.[6] We found this blood to contain 0.6 c. c. oxygen per hundred cubic centimeters blood.

The oxygen content of the venous blood varies slightly according to the part of the body from which it comes. During absolute rest in bed and before breakfast the blood coming from the heart will have more oxygen abstracted from it than blood which has passed through the capillaries of resting organs, like the arms, legs and trunk. The venous blood coming from the brain will also contain less oxygen than blood coming from an active organ like the heart. Metabolism in the portal area is not at its height during morning rest. It is safe to assume that although an active organ like the heart might possibly under the conditions of a very low oxygen content of the arterial blood abstract nearly all the oxygen, yet it is not very probable that this would occur, for a glance at the dissociation curve of oxyhemoglobin[7] shows that when the oxygen content has dropped to 10 per cent. of its normal maximum content[8] then the diffusion pressure is only 10 mm.[9] or about one tenth of the mean diffusion pressure in the capillaries and one fifth the average diffusion pressure in normal venous blood. The speed of diffusion is lowered to a point where oxygen must leave the blood in the capillaries very slowly and it is doubtful if under the conditions of increased velocity of flow in this case, which we shall prove in this paper, the last vestiges of oxygen can be

6. Van Slyke: J. Biol. Chem. **33**:127, 1918.
7. Bohr, Hasselbach and Krogh: Scand. Arch. f. Physiol. **16**:402, 1904.
8. In this case 0.4 c.c. per hundred centimeters blood.
9. Assuming that the partial pressure of oxygen in the tissues is zero.

abstracted. That this reasoning is justified not only theoretically but also experimentally is shown by the fact that in a series of determinations of the oxygen content of the venous blood of cases of pernicious anemia and heart failure, values under 20 per cent. of the arterial content were never found by Plesch [10] by means of a method whereby the oxygen content of all the blood flowing into the right heart is determined. Moreover, an experiment performed by Lundsgaard [11] on himself shows that when the oxygen pressure falls the oxygen diffusion from the capillaries slows up very much and the last vestiges of oxygen leave the capillaries very slowly. In this experiment a sample of venous blood from the arm was taken and analyzed after which a compression of 30 mm. was produced in the upper arm by means of a blood pressure cuff for two minutes. After slowing up the stream by this means, a pressure 30 per cent. greater than systolic pressure was produced for two minutes thus reducing the velocity of the circulation to nearly zero. The venous oxygen in the arm vein blood was now 45.5 per cent. of the arterial, whereas before the stasis it was 76 per cent. After four more minutes of this almost complete stasis the oxygen content had fallen only to 40 per cent. We can see from this experiment that when the partial pressure of the oxygen in the capillaries falls to about 2 mm. or the oxygen content to about 40 per cent. of the arterial pressure that diffusion is so slow that even in marked retardation of the rate of flow it is nearly impossible to get an abstraction of oxygen to below 10 per cent. We, therefore, feel justified in stating that in no part of the venous system of our patient did the oxygen content fall below 0.2 c.c. per hundred cubic c. c. blood. If the oxygen content of the arm vein blood is 0.6 c.c. per hundred cubic centimeter blood, then it is safe to assume that the venous blood from the legs and brain is not much less. If, therefore, we put down 0.4 c.c. as the mean oxygen content of 100 c.c. blood, in this case we certainly are not making an error of more than 0.2 c.c., or $\mp$ 10 per cent. Using this value we find that each hundred cubic centimeters blood gives up $2.4—0.4 = 2.0$ c. c. oxygen during its passage through the capillaries. If, therefore, the total oxygen consumption per minute is 213.5 c. c., then it follows that $\frac{213.5}{2.0} \times 100$ c. c. of blood must leave the lungs and flow through the capillaries of the body in each minute. A minute of 10.7 liters is about two and one-half times the normal minute volume for a man of this size and weight.[12]

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10. Plesch: Ztschr. f. exper. Path. u. Therap. **6**:395, 1909.

11. Lundsgaard: J. Exper. Med. **30**:278, 1919. It is only fair to state that Lundsgaard did not draw these conclusions.

12. Plesch: Loc. cit.; also Krogh and Lindhard: Skand. Arch. f. Physiol. **27**:100, 1912.

In other words it is largely by increased heart output that the low oxygen content of the blood is compensated for.[13]

As the patient's pulse rate was 76 at the time of these determinations we see that the output of each chamber of the heart during systole is 140 c. c., or about 2.5 times the normal output for a man of this size, at rest. It is interesting to determine some of the factors concerned in this increased velocity of blood flow and the work thrown upon the heart. Alder has shown that when the number of normal red cells in the blood is reduced to 13 per cent. of the normal the viscosity falls to 43 per cent. of its previous value. In a determination on pernicious anemia blood with a red count of 1,080,000 he found the viscosity coefficient 2.5, whereas for normal blood it ranges between 4.5 and 6.5. As no determination was done on the plasma alone in this case it is necessary to interpolate to find the percentage reduction of viscosity of the whole blood in this case. We know from his determinations that only 40 per cent. of the normal viscosity of blood is due to the plasma, 60 per cent. being due to the corpuscles. By a simple algebraic calculation[14] we find that 4.8 would be the viscosity coefficient if the number of corpuscles were 5,000,000. By another simple calculation we reckon that if the number of red cells in Alder's case of pernicious anemia had been only 500,000, as in our case, the viscosity coefficient would have been 2.2, or a reduction of the viscosity to 45 per cent.[15] of its normal value. This means that if the blood pressure and the cross section of the vessels remains the same, the velocity must have been increased 2.2 times. As the blood pressure in our case at this time was 105 systolic and 69 diastolic we must reckon that the decrease in viscosity and the decrease in blood pressure together condition in this case an increase of only 1.9 times in the velocity of the blood. If the minute volume is increased 2.5 times, there must have been in addition to the decrease in viscosity an increase in the effective cross section of the vessels. A 20 per cent. increase in the diameter of the vessels would be sufficient to increase the velocity from 1.9 to 2.5 times the original velocity, if the pressures and viscosity change as above calculated.

Two of our observations and one theoretical conclusion seem to argue against any increase in the cross section of the vascular tubing. Determinations of the plasma volume and the blood volume according

13. This statement with proof is also found in Plesch, loc. cit., and in Lundsgaard, loc. cit.

14. $0.4\,n + (0.6 \times 0.2)\,n = 2.5$, therefore $n = 4.8$.

15. The reason that the reduction in viscosity in this case of pernicious anemia was less than the reduction due to reducing the number of normal red cells is that the average size of a red cell is greater in pernicious anemia and the larger the cell the greater the viscosity of the fluid in which it is suspended.

to Rowntree's [16] method gave 5.2 per cent of body weight for plasma volume or a little more than the normal average for plasma volume. Because of the small corpuscular volume the total blood volume was only 5.4 per cent. of the body weight, or considerably less than the average normal. Therefore, the total blood content of the tubing was less than the normal, and it would seem hardly probable on first thought that the effective cross section of the tubing could be larger. Besides we know that the filling of the heart must be considerably greater in order to get the large output we have calculated. Moreover, frequent examinations of the finger capillaries with the method of Lombard [17] showed both a very marked contraction of the capillaries and fewer open capillaries. It is impossible to check up the lumen of all the vessels but the above observations do not mitigate against the assumption that the effective cross section of the vessels was greater, thus causing increased velocity, and at the same time the total volume content of the whole vascular tubing was diminished to correspond to the decrease in blood volume and the increased filling of the heart itself. For Poisseulle's formula for the velocity of blood flowing through tubing is $\frac{V = k.pr^4t}{l}$ where v is velocity, k is the reciprocal of viscosity, p is blood pressure, r is the radius of the section of tubing under consideration, t is the time and l the length of the tubing. As the radius is in the numerator in the fourth power and l is in the denominator in the first power it is easy to see how by increasing the diameter of the short capillary area and at the same time diminishing the lumen of the long arterial and arteriolar area both the effective resistance and the total volume of the tubing may be reduced at the same time.

Our capillary observations showed that some of the skin capillaries are remarkably reduced in diameter. We believe that this is one of the compensatory factors for securing increased flow of blood in more important organs where metabolism is greater. As observed by the microscope the flow in the skin capillaries was very slow but this is easily explained for the diameter of these capillaries was less than half of that of other patients and normals. Toward the end it was approximately one third the diameter of our own capillaries. On the other hand, the vital organs at necropsy impressed the pathologist as being more than normally filled with blood.

It is interesting to calculate the work done by the heart per minute and its oxygen consumption. In calculating the work of the heart we shall make use of Evans' [18] formula $W = \frac{7}{6} Q R + \frac{QV^2}{G}$, where Q is the minute volume, R is the combined aortic and pulmonic blood pressures

16. Rowntree, Geraghty and Keith: Arch. Int. Med. **16**:547 (Oct.) 1915.
17. Lombard: Am. J. Physiol. **29**:335, 1912.
18. Evans: J. Physiol. **52**:6, 1918.

in terms of a water column,[19] V is the linear velocity calculated from the aortic and pulmonic cross section, the minute output, and the actual time during which blood is flowing out of the ventricles, and G is the constant of gravity acceleration. We find that the heart performs 18.5 kg.m. of work per minute necessitating an oxygen consumption of 30.5 c. c. per minute,[20] or one seventh the total oxygen consumption of the body. If we assume that the venous blood leaving the coronary veins has an oxygen content of only 0.2 c.c. per hundred cubic centimeters, then we can reckon that the coronary circulation is 1.48 liters per minute, an enormous flow. Even if we assume that the oxygen content of the whole venous blood of our patient was 0 we are compelled to calculate a minute volume of 9.5 liters for the circulation and an oxygen consumption in the heart of 26 c. c. each minute. Even under these conditions the coronary flow would be 1,190 c. c per minute. It would be necessary to have a coronary circulation of 1.2 liters per minute to supply even this oxygen need. Evans has shown that the heart during the performance of very severe work must have a coronary circulation of about 850 c.c.[21] With blood of the viscosity of our patient's such a flow would become 1.87 liters, so that it is not at all impossible as at first it might seem. Of course, it is possible that the efficiency of the heart is greater than 30 per cent., but from Evans' [22] work we would assume that 30 per cent. is the highest mechanical efficiency of the human heart.

Our calculation shows that the heart may very easily suffer from lack of oxygen, especially if the patient is not at absolute rest. There is very good support in this paper for the pathologist's contention that the heart muscle changes of pernicious anemia are due to lack of oxygen.[23]

CONCLUSIONS

1. In severe anemias increased minute volume is the outstanding compensatory mechanism for loss of oxygen carrying power of the blood.

2. In a case of severe pernicious anemia the minute volume was increased about 250 per cent. and the systolic output in the same degree.

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19. Evans uses 1.7 for R, in persons of normal blood pressure = 120. As the blood pressure in our patient was 105 we have used 1.5 for R.

20. Assuming that the mechanical efficiency of the heart is 30 per cent. and respiratory quotient 0.8.

21. Evans: J. Physiol. **47**:407, 1914.

22. Evans: J. Physiol. **52**:6, 1918.

23. Laboratory data of interest: CO_2 tension in alveolar air 37 mm.=5.2 per cent. Hydroxybutyric acid in blood 1.2 mg. per hundred cubic centimeters. Other acetone bodies, 0.53 mg. per hundred cubic centimeters. CO_2 combining power of blood, 62.6 c. c. per hundred cubic centimetres plasma. CO_2 content of blood, 51.3 c. c. per hundred c. c. plasma.

3. The increased blood velocity was very largely due to lowered blood viscosity, this being lowered to 45 per cent. of its normal value.

4. Another factor was increased effective cross section of the vascular tubing.

5. Microscopic examination of the skin capillaries showed that they were contracted down to half the normal diameter or less, thus determining a lessened blood flow through the skin and a larger flow through other organs. The lessened quantity of blood in the skin is certainly one factor in the degree of paling of the skin.

6. The coronary circulation is at the upper limit of the possible being about as large as that found in very severe work. There is a very great possibility that when a patient with severe anemia tries to work that anoxemia of the heart muscle is produced. The pathologic changes in the heart muscle in pernicious anemia may well be due to lack of oxygen.

A HITHERTO UNDESCRIBED TUMOR OF THE BASE OF THE AORTA*

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Tumors of the heart are not commonly met with and their clinical diagnosis up to the present time has been difficult, if at all possible, to make. Tumors of the aorta are much less frequent than those of the heart. Newer clinical diagnostic methods are promising much, however, in the early recognition of these cases. The tumor of the aorta attached to the heart which we found in our case has no counterpart in the literature. It became of interest, therefore, to describe this case not only from its clinical but also its anatomical aspects.

REPORT OF CASE

N. R., a white male, married, aged 54, was admitted to Barnes Hospital on the service of Dr. George Dock for the first time, June 26, 1918. The chief complaint at that time was shortness of breath occurring in paroxysmal attacks off and on for over fifteen years.

Family History.—This was unimportant, except that one brother, who had died of pneumonia, was supposed to have had "heart trouble."

Personal History.—The marital history was insignificant. The patient had been married eight years, he had one child, a boy of 6 years, living and well. His wife was living and well and had had one miscarriage.

Past History.—He had not had chorea, diphtheria, scarlet fever, pneumonia or tonsillitis. He had had measles, pertussis and typhoid fever in childhood but had recovered from these without complication. He had had gonorrhea at 28, and a "hard chancre" of the urinary meatus, with bubo and inflammation of the testicles, at 29. He had been treated for syphilis by local applications and by mouth. No secondary lesions developed. "Smothering attacks" with shortness of breath, which he termed "asthma" had troubled him for fifteen years. These attacks would come on after exertion and were accompanied by palpitation and the appearance of a dusky gray color. He had taken three or four glasses of whisky, smoked two to three pipefuls of tobacco, and drank two to three cups of coffee daily for years.

Present Illness.—The trouble that brought him to the hospital was more or less dyspnea which gradually became exaggerated following an attack of "rheumatism" in February, 1918. He began to notice difficulty in breathing and wheezing, particularly at night, when lying in bed; no palpitation or pain was noticed and the symptoms were relieved by his getting on his feet. The attacks of dyspnea on exertion which he had had for years had grown more severe. His feet had been swollen for a week and there had been blueness of the lips and face during several of the attacks. The patient fainted once. He had also had pain in the epigastrium which radiated down into the abdomen.

Physical Examination.—The patient had a robust frame with moderately heavy musculature and thick panniculus, weighed 185 pounds and measured 70 inches in height. He walked into the ward but was very dyspneic. There

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was a dusky ashen pallor about his face while the rest of the body was cyanotic. On reclining the face became very cyanotic. Orthopnea was noted and the respiration was Cheyne-Stokes in type. The patient would drop off to what appeared to be sleep during the apneic periods. The veins of the neck were slightly engorged but there were no abnormal pulsations. The lungs were negative, except for many crackling râles at both bases posteriorly.

Heart: The heart was defintely enlarged. The apex impulse was not well localized but was felt best about 15 cm. to the left of the midsternal line in the fifth intercostal space. There was a general precordial heave without a strong impulse on palpation. No thrills were felt. The cardiac outline to percussion was 2.5 cm. to the right and 2.5 cm. to the left of the midsternal line in the first intercostal space; 3.5 cm. to the right and 4.5 cm. to the left in the second intercostal space; 4 cm. to the right and 9 cm. to the left in the third intercostal space. What was considered to be liver dulness was elicited on the right side below the third intercostal space, while to the left the figures of the outer cardiac dulness were: 14 cm. in fourth intercostal space; 16 cm. in fifth intercostal space, and 17 cm. in sixth intercostal space.

The contractions were regular and rapid. A systolic murmur was heard at the apex. This was transmitted toward the axilla, but not toward the sternum. Both sounds were accentuated at the apex. The pulmonary second sound was accentuated and louder than the aortic second sound. The blood pressure was from 110 to 120 mm. Hg. systolic, and from 100 to 85 mm. Hg. diastolic.

The pulse was regular and rather small. The radial and brachial artery walls were very much thickened, but not calcareous. The feet and legs were oedematous.

Abdomen: The abdomen was above the costal margin. There was distention of the superficial veins in the left hypochondrium. Tenderness was elicited in the epigastrium. The liver edge was found to be 8 cm. below the costal margin in the midclavicular line. Tenderness was noted all over the enlarged liver.

There was a linear 2 cm. scar of the old bubo in the left groin. The right lip of the urinary meatus was large and verrucous. The patient said that the "hard chancre" had been at this site. A small varicocele was found on the left side. The prostate was of moderate size, thickened throughout and adherent.

No abnormal reflexes or neurologic signs were elicited.

The patient was seen by Dr. G. Canby Robinson who found a general precordial heave in the region of the apex with no local heave but a definite tap. The heart borders extended 5.5 cm. to the right and 16.5 cm. to the left of the midsternal line. The heart sounds were blurred and distant. A faint nontransmitted systolic murmur was heard at the apex. The pulse was palpable with difficulty and counted 116 per minute. The pulmonary second sound was accentuated.

The electrocardiogram showed right ventricular preponderance and the chest plate showed right sided hypertrophy. Aside from these there were, however, no other signs of mitral stenosis.

A dose of 10 c.c. tincture of digitalis was administered and the regular rhythm became absolutely irregular within twenty-four hours. A slight pulse deficit was noted at that time and the difference in the force was more striking than the arrhythmia, but no pulsus alternans was ever demonstrated. The pulse later became regular and the edema disappeared. The liver, on the other hand, at the time of discharge remained 8 cm. below the costal margin in the parasternal line. The patient was given a prescription for 10 minims tincture of digitalis to be taken three times a day and discharged improved, July 20, 1918, to return to the Outpatient Department for observation.

Clinical Laboratory Findings.—Blood: The red blood cells numbered 4,472,000; white blood cells, 7,100; hemoglobin, 75 per cent. The differential smear showed polymorphonuclear neutrophils, 73 per cent; lymphocytes, 20 per cent., and large mononuclears and transitionals, 6 per cent. The blood Wassermann reaction was negative. The blood nonprotein nitrogen was 78 mg. per hundred c.c.

Urine: The specific gravity varied from 1.018 to 1.026. The volumes were small. Occasionally the night volume was increased over the day volume. There were also traces of albumin, and numerous hyaline and finely granular casts. Fifty-three per cent. of phenolsulphonephthalein was excreted in two hours.

Electrocardiograms:

1774; June 27; auricular flutter; well marked right sided preponderance.

1770; June 28; auricular flutter; well marked right sided preponderance.

1786; July 1; auricular fibrillation (24 hours after administration of 10 c.c. tincture digitalis).

1797; July 5; auricular flutter in part of the record; impure in another.

1801; July 7; auricular flutter; arrythmia suggesting varying degrees of block; auricular rate, 250; ventricular rate, 109.

1803; July 10; normal rhythm reestablished; right ventricular preponderance (suggesting mitral stenosis); S wave in Lead 1 very short again; negative T waves in all leads; diphasic P in second and negative P in third leads; rate, 102; P.R. 0.22 sec; Q R S, 0.08 second.

1815; July 11; one left ventricular extrasystole, otherwise as 1810. Depth of S wave in Lead 1 increasing.

There were no changes in the subsequent curves taken while the patient was in the hospital. The numbers and dates of these were as follows: 1824, July 13; 1831, July 15; 1837, July 16; 1843, July 17; 1849, July 19; 1855, July 20.

Record of Outpatient Department: The patient was seen at frequent intervals in the Outpatient Department where 10 minims tincture digitalis was ordered to be taken three times a day.

July 30: The cyanosis was marked. The heart action and the pulse were regular and equal.

August 15: The cyanosis remained the same. The heart action and the pulse were regular and equal.

September 3: The cyanosis was less, but there was puffiness about the eyes. The heart was regular at 84 per minute. The urine showed pus cells.

November 4, the patient was seen by Dr. Robinson, who found the outer cardiac dulness to be 4 cm. to the right and 17.5 cm. to the left of the midsternal line. He also noted an arrhythmia of a peculiar type associated with periods of regular rhythm. There was also a dropping out of beats without any evidence of premature contraction.

Electrocardiogram 2027, taken at this time, shows a curious type of arrhythmia suggesting a shift of the pacemaker in the junctional tissue, delayed auriculoventricular conduction and slight left ventricular preponderance.

December 9, Dr. Robinson noted that the patient was somewhat cyanotic. The point of maximum impulse was 14 cm. to the left in the fifth intercostal space. The limits of cardiac dulness were 4.5 cm. to the right and 14 cm. to the left of the midsternal line. A very faint systolic murmur was heard at the apex. The heart rhythm was irregular. It had a rate of 66 with groupings of three beats heard at times with regular periods. The liver was not felt and there was no edema of the ankles.

Jan. 13, 1919, another note by Dr. Robinson states that the ventricular rate is 74, there is no deficit of the pulse and that the patient complains of pain in the neck. Electrocardiogram 2163 shows: a tendency to left ventricular preponderance; delayed A-V conduction; P waves flat in Lead I, diphasic with deep negative phases in Lead II, negative and notched in Lead III; T waves upright in Leads I and II, inverted in Lead III; R waves notched in Lead III, becoming tall with the lowering of the diaphragm; Q R S interval lengthened; and periods of striking irregularity marked by changes in the P-R interval. Changes in the form of P waves are also noted. In two instances by changes in the form of R waves there is the appearance of a change from a right to a left ventricular preponderance. The P-R interval is 0.24 second. The rate is 78.

Second Admission.—March 4, 1920.

His complaint at the second admission, in addition to his shortness of breath, was pain in the lower part of the chest. He had been doing quite well until six weeks before admission when suddenly he had a "dizzy spell," his right leg became numb, and he fell to the ground. The attack lasted but a few minutes, his arm was not involved, there was no loss of consciousness or aphasia and he was able to walk within ten minutes. His dyspnea had been gradually getting worse and had been very severe for a week. After working hard, moving furniture, he had considerable difficulty in breathing. Often at nights he had to get up out of bed and sit in a chair for a few hours before he could recline and sleep.

Physical Examination.—This was very similar to that of the previous admission. The superficial veins, however, were much more prominent. They were engorged and tortuous over the manubrium below the right nipple and over the precordium. There were numerous varicosities over the right and left lower chest. Several large varicose veins were noted over the abdomen about the umbilicus and in the right hypochondrium. The leg veins were likewise varicose.

The findings in the lungs, heart and liver were as described previously. The heart was regular and rapid. The right cardiac border was found to be from 3.5 to 5.5 cm. to the right of the midsternal line until the seven-foot roentgenogram showed a large bulge 11 cm. to the right of the midsternal line. After this the percussion also routinely revealed a dulness from 10 to 11 cm. in this direction. According to the fluoroscopic examination made by Dr. Sherwood Moore and Dr. Frank N. Wilson there was also a clear space between the heart and the aorta in this region. This they thought ruled out an aortic aneurysm situated on the descending aorta behind the heart. This large shadow at the right border of the heart was seen to flicker but the movement was so slight that the observers could not be sure that it was not imaginary. This wide shadow to the right also gave the impression of a widely dilated right auricle suggesting the possibility of tricuspid stenosis, but there were no other signs to bear this out.

Dr. Robinson interpreted the roentgenogram as showing apparently a great dilatation of the right ventricle. This could not be reconciled, however, clinically with the signs and symptoms present. The latter were also different from those of aneurism of the heart.

Dr. Dock commented on the conspicuous wavy epigastric pulsation and the dilated superficial veins and suggested that a tumor could not be ruled out as other possibilities such as tricuspid stenosis and cardiac and aortic aneurism had been. An exploratory puncture was not made as had been suggested.

During the period of regularity the rhythm was shown by the electrocardiograms to be auricular flutter, with two to one block. Vagus experiments were done which showed the characteristic marked lability of the His bundle to vagus stimulation in this condition. Vagus stimulation by direct or ocular pressure stopped the ventricles for four to five series of four to twelve auricular beats. There was ventricular standstill for as long as three seconds (Fig. 2).

Dr. Robinson suggested a dose of 20 c.c. tincture of digitalis and repeated vagus tests. The digitalis at first produced irregular blocking with four to one rhythm. Vagus pressure caused a greater change than before digitalization. In one run the ventricles stood still for twenty-five auricular beats or about six seconds. Other series of long runs of 6, 8, 10 and 16 to one rhythm were obtained. Auricular fibrillation then appeared and persisted. The patient was discharged clinically improved, March 19, 1920.

Clinical Examination and Laboratory Data.—Blood: The red blood cells numbered 6,470,000; white blood cells, 6,950; hemoglobin, 100 per cent. The blood Wassermann was negative. Urine: The specific gravity varied from 1.020 to 1.038. The urinary output was small. No albumin or casts were found in any urine specimen. The phenolsulphonephthalein test showed 65 per cent. excretion in two hours.

The blood pressure was from 100 to 120 mm. Hg. systolic, and from 70 to 95 diastolic.

A seven-foot roentgenogram of the heart (Fig. 1) showed a large sharply outlined circular shadow projecting to the right of the midclavicular line.

The cardiac dimensions measured on the seven-foot teleroentgenograms were: Before digitalization, M. R., 11 cm.; M. L., 12.5 cm.; L, 22.5 cm.; A, 7 cm. After rest in bed and digitalization, M. R., 10 cm.; M. L., 12.5 cm.; L, 23 cm.; A, 6.5 cm.

Electrocardiograms (Fig. 2):

3716; March 7, 1920; auricular flutter; auricular rate, 266; ventricular rate, 128.
3725; March 8; auricular flutter; vagus experiments (Fig. 2).

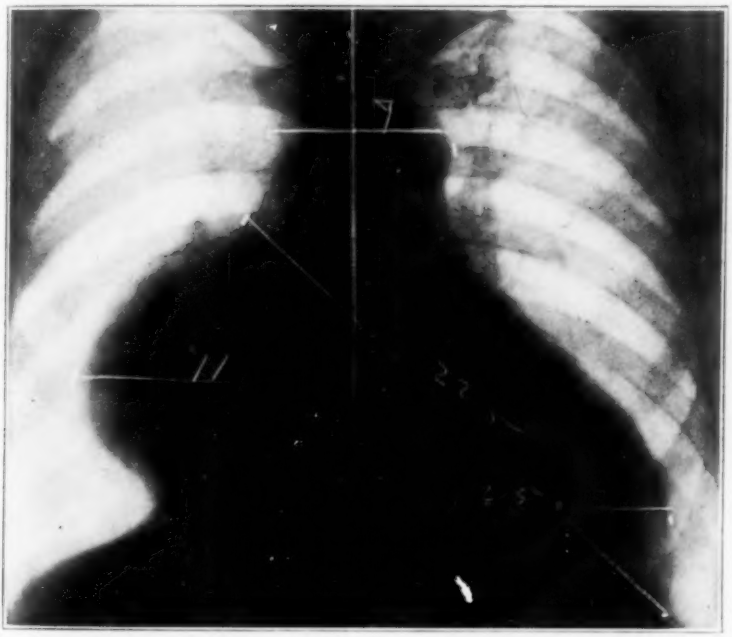


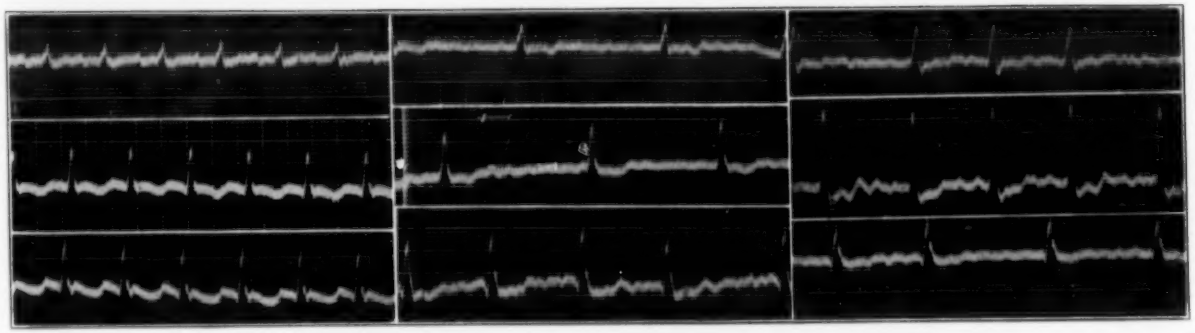
Fig. 1.—Seven foot roentgenogram of the chest made at the time of the second admission, March, 1920.

3739; March 9; three hours after digitalization, auricular rate, 256. Mixture 2 : 1, 3 : 1 and 4 : 1 block.
3740; March 9; six hours after digitalis; vagus experiments.
3741; March 10; fifteen hours after digitalis.
3750; March 10; auricular fibrillation twenty-eight hours after digitalis.
3769; March 12; auricular fibrillation.
3783; March 16; auricular fibrillation.

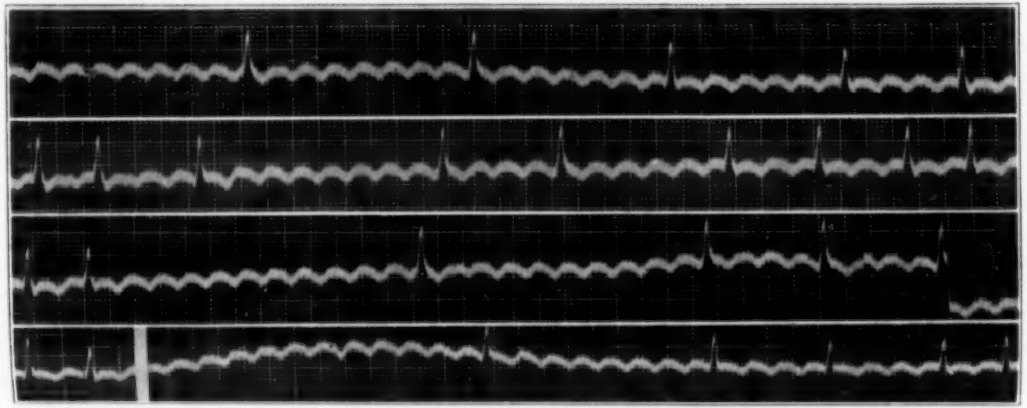
Final Notes April 3, 1920.—After leaving the hospital the patient, contrary to order, did rather heavy work. He had not been any more dyspneic than usual, but had some edema about the ankles each evening. He did not take the tincture of digitalis regularly as it had been prescribed. It was not known whether his pulse was regular or irregular. He had been complaining for a few days, but

Auricular Flutter

3716 3750 3783



Vagus Pressure Experiments



R. & L. 8-7-7-5
Pressure

R. & L. 8-4-6-3
Pressure

R. 11-10-4-4-3
Pressure

L. 12 + ?-8-4-4-2
Pressure

Fig. 2.—Electrocardiographic tracings.

refused to return to the hospital. April 2, he carried an iron range (stove) up three flights of stairs. In the evening he felt more "blue" than usual, but went to sleep apparently well. During that night he apparently did not struggle, at least his son sleeping with him was not awakened. On the following morning, however (April 3), he was found dead in bed. The body was slightly cool, quite cyanotic, especially the face, but rigor mortis had not set in.

NECROPSY REPORT

Permission for a complete necropsy could not be obtained. An examination of the heart alone was allowed. This was removed after the body had been embalmed. We saw it for the first time when it was brought to the laboratory. We are grateful to Dr. Robinson for his effort in gaining permission for us to examine this organ.

Heart: The organ is greatly enlarged, and a large tumor mass, the size of a large orange, is attached to the superior wall of the right auricle, to the tissue of the auricular septum, to the sides of the aorta and pulmonary artery. The attachments to the aorta and pulmonary artery are loose. The firm attachment is to the auricular wall. The fibrous tissue of the pericardium of the heart is continuous with the tumor. The muscle of the auricular wall beneath the tumor is atrophic and apparently not continuous with it. The attachment to the auricle does not appear to be a primary one but secondary to the irritation of the tumor lying on the auricle. The heart with the tumor weighs 945 grams.

The heart is enlarged, the hypertrophy being more marked in the left than in the right ventricle. The tricuspid valve measures 14.5 cm.; the mitral, 11 cm.; the aortic, 7.5 cm.; the pulmonary, 10 cm.; the muscular portion of the left ventricle wall measures 14 mm.; that of the right, 4 mm.

The mitral valve is uniformly thickened throughout and near its base are several fibrous and fatty placques, a few of which contain gritty material. The papillary muscles are much enlarged and there are several areas of fibrous thickening in the endocardium of the left ventricle. The aorta is normal in size. There are a few small fibrous and fatty placques in the intima of the aorta. The endocardium of the right ventricle and auricle show nothing of interest except at the attachment of the tumor. Here the endocardium is in close contact with the hard, gray, opaque wall of the tumor mass, which can be seen through it. The muscle fibers are largely missing in this region.

The myocardium of other portions of the heart, aside from the hypertrophy, show nothing of interest.

The epicardium over the whole of the heart contains a considerable amount of fat. The coronary arteries are straight and aside from the first few centimeters of their courses show nothing of interest. In the first centimeter of the left coronary there are numerous fibrous and fatty placques in the intima. Similar changes are seen in the first 5 cm. of the right coronary artery.

The orifices of these vessels are slightly constricted and there are several fibrous and fatty placques in the intima of the aorta immediately about them.

Just to the right of the orifice of the left coronary artery and in the aorta and just above the sinus of Valsalva is a cone-shaped pouch which extends inwards and appears to end blindly (Fig. 4a). It is 1 cm. deep and the diameter of the inner opening is 1 cm. Except for its shape it has the appearance of a small aneurism. There are several fatty and fibrous placques in the intima lining it.

Lifting the tumor away from the aorta reveals the outer wall of this pouch, which is seen to be continuous with a tough cylindrical shaped cord of tissue which passes directly to the wall of the tumor to disappear within it (Figs. 3 and 4b).

This slender cylindrical shaped cord is evidently the pedicle of the tumor, and on close inspection is found to be composed externally of a tough gray tissue like that of the aorta or one of the large arteries. It has, however, no evident open lumen, but its center is composed in places of a gelatinous and in other

places of a glistening gray material. It measures 4 cm. long and ½ cm. in diameter. It looks like an occluded anomalous arterial branch.

The tumor is ovoid in shape and measures 12×9 cm. It has a tough hard outer wall and is filled with a greasy necrotic material which everywhere glistens as if it contained crystals. A smear of this necrotic material shows large numbers of rhombic plates with notched corners. The outer tough wall is thickened at the point of insertion of the pedicle. Here there is a large necrotic fragile nodule which extends in and replaces a part of the soft greasy material (Fig. 4c).

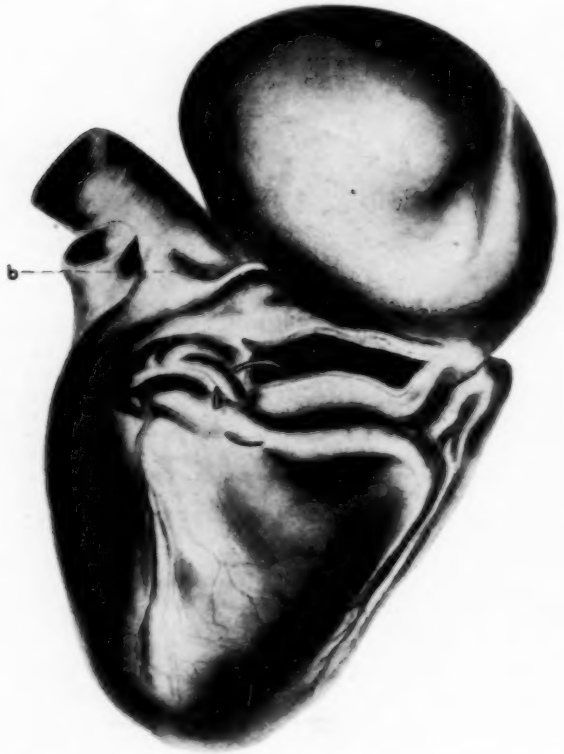


Fig. 3.—Semidiagrammatic drawing of the heart showing the tumor.

The remainder of the wall is thin. It measures from 1 to 2 mm. in thickness. This wall is seen to be divided into several layers. An outer one resembling muscle in many places, a second fibrous looking layer, and an inner layer which is in contact with the glistening greasy content. This last layer appears to be composed of a gelatinous material which in places is streaked and mottled with gray and yellow opaque lines and splotches.

From the gross description alone it was evident, therefore, that the tumor was not of auricular but probably of aortic origin. It had arisen from an anomalous arterial like branch of this vessel.

Microscopic Examination.—The microscopic examination of the heart shows muscular hypertrophy and nodular thickenings of the endocardium of the left ventricle. These nodules are fibrous and the centers of the larger ones are necrotic.

Atheromatous nodules of small size are present in the intima of the aorta. The media of the vessel appears normal but there are collections of lymphoid cells about a few of the vessels of the adventitia.

The wall of the aneurysmal-like pouch which marks the point of origin of the tumor pedicle (Fig. 5) is much like that of the aorta. It has a well formed intima, media and adventitia. The intima is irregularly thickened and fibrous

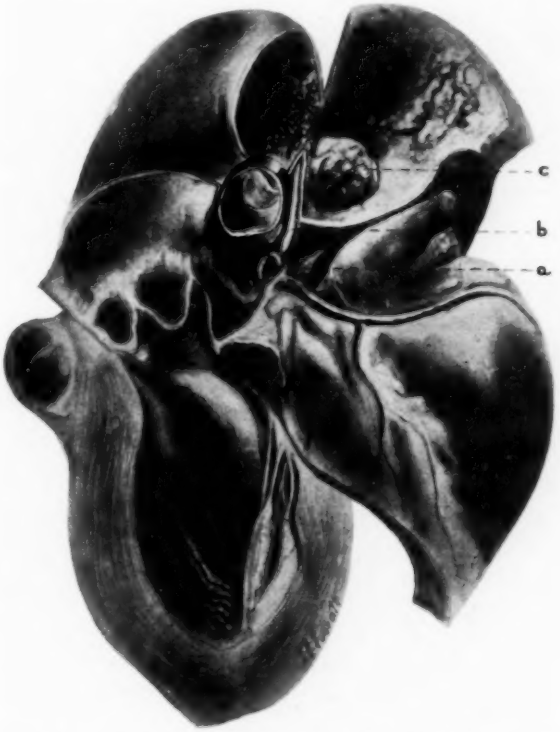


Fig. 4.—Similar drawing showing the heart and tumor opened. The lips of the aneurysmal pouch are exaggerated. They are flat and smooth.

in places. The outer portions of the media also show fibrosis and in one place this layer contains a large calcified placque. The muscle cells and the elastic tissue of the inner portions stain sharply. At the boundary between the adventitia and the media there are a few lymphocytes and there are also collections of these cells about a few of the larger vessels of the adventitia.

The pedicle has the structure of an artery with an excessively thickened intima which obliterates the whole of the lumen (Fig. 6 and 7). The media is well formed. It has a sharply defined internal and a poorly defined external elastic lamella. There is a slight increase in fibrous tissue within it but also

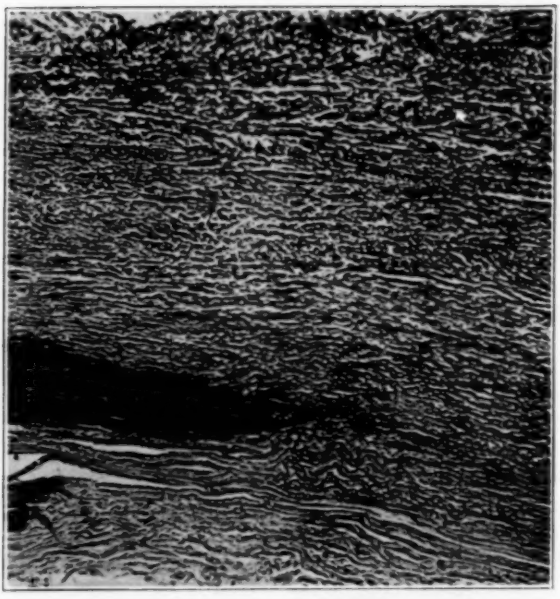


Fig. 5.—Photograph of a cross section of the wall of the aneurysmal pouch.

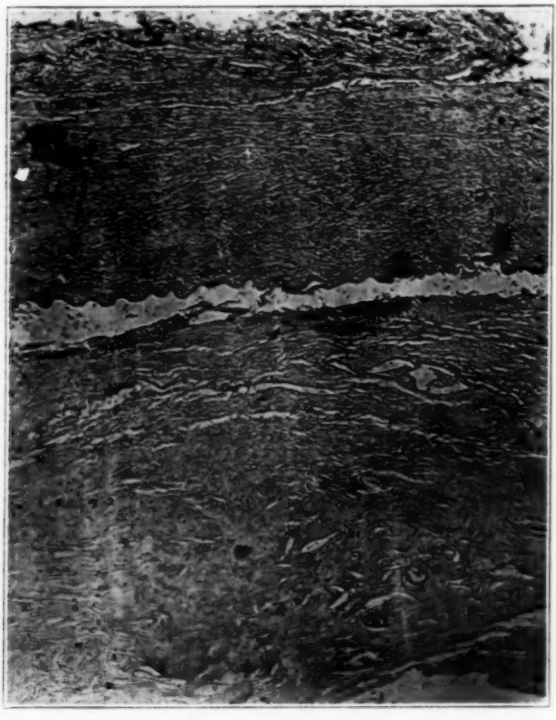


Fig. 6.—Low power photograph of one half of a cross section of the pedicle

sharply staining muscle cells and elastic fibers. The excessively thickened intima is composed of loose fibrous tissue with a finely granular intrafibrillar substance. In places it contains a few polyblastic cells and in other places it is degenerated and reduced to a homogenous granular mass containing numbers of open ovoid, circular and rhombic shaped spaces like those of the center of the tumor.

Sections from all parts of the tumor show the same general structure (Figs. 8 and 9), an outer tough sharply staining thin fibrous wall which grades off gradually or in places sharply into the large granular bluish and pink staining mass. This mass contains large numbers of open spaces which vary in shape. Many are spindle shaped (Fig. 10); others are ovoid, circular or rhomboid in shape.

Fig. 7.—Higher power picture from another section of the pedicle.

The outer fibrous wall contains large numbers of polyblastic, plasma and small mononuclear cells (Fig. 8A). A few of these cells or shadows of them are seen deeper in the hyaline and necrotic portions (Fig. 8 and 9 B). Calcium deposits are also not uncommon in the hyaline portions of the wall (Fig. 8 B).

Sections through the auricular wall at the attachment of the tumor show no direct connection of the tumor with this part of the heart. The tumor wall is sharply defined and connected with the heart wall by loose fibrous tissue. In a few places atrophic and degenerating muscle fibers are seen between the tumor and the endocardium.

The picture as described in this tumor is one of a progressively degenerating fibrous wall of inflammatory origin. Leaving aside the inflammatory cells it is the picture of the ordinary atheromatous patch of the aorta. There is no evidence that it is or has been a neoplasm. It is rather a massive atheromatous tumor of what appears to be an atypical arterial branch of the aorta. This branch or pedicle has the appearance of an artery obliterated by an excessive proliferation of its intima.

Fig. 8.—Photograph of a section taken through the wall of the tumor. A is the outer sharply staining area. B is the inner hyaline and fibrous layer.

The pouch at the origin of the tumor pedicle from the aorta has a well formed wall resembling that of the aorta. It looks like a simple dilatation of the wall of the aorta at this point rather than an aneurism. The changes in the wall of this pouch and in the aortic wall are suggestive of a generalized chronic degenerative and inflammatory disease of the vessels. The nodules as those described in the left ventricle have been also definitely associated with syphilis by some. It is possible in this case, however, that these changes in the aorta may have been secondary to the irritation of the tumor.

Fig. 9. — Photograph of a section of another part of the wall of the tumor. A is the outer sharply staining layer. B is the inner hyaline and necrotic layer.

Fig. 10.—Open spaces in the central part of the tumor mass.

CLINICAL SUMMARY

The case, as is evident, is a most unusual one. The clinical symptoms are largely those of a tumor of the heart while pathologically it is questionable whether the tumor is nothing more than a part of a more generalized inflammatory disease of this organ.

The patient was a chronic alcoholic. The supposed syphilitic infection at 28 years of age seemed to antedate any of the symptoms. The "smothering" and "asthmatic" attacks and mild cardiac symptoms followed this more or less closely. Aside from these facts, as well as the long duration of the disease, the symptoms might well have arisen entirely from the presence of a neoplasm. The symptoms were those of a gradually progressing myocardial change.

The reason for the insidious exaggeration of symptoms following "rheumatism" four months before admission is not clear. The dyspnea and the wheezing on reclining, relieved by arising, might well be explained as myocardial resulting from tumor pressure.

In the original physical examination, the observation of an ashen pallor, conspicuous cyanosis of the body and dilatation of the superficial abdominal veins on standing and the spread of the cyanosis to the face on reclining might have resulted from a tumor pressing on the venae cavae. Cheyne-Stokes breathing was present as a part of the cardiac syndrome. The dulness to the right and below the third rib which was taken to be that of the liver was probably due to the tumor. The roentgenogram of the chest taken at this time showed a shadow in this region which appears to be clearly the same enlargement that produced the striking teleroentgenogram which led to the special interest in the case and the provisional diagnosis of cardiac tumor.

On the second admission there was the added complaint of pain in the lower chest which might have been associated with the tumor. The sharply outlined shadow extending 11 cm. to the right of the midsternal line was considered one of three things: an aneurysm of the heart, a dilated right auricle from tricuspid stenosis or a tumor. The latter was not ruled out, while aneurysm and dilated auricle were considered improbable because of the patient's general condition and the physical findings. Fluoroscopic examination showed no definite movement or pulsation of this huge shadow.

The electrocardiograms in this case revealed interesting findings. The curves first showed auricular flutter which after digitalization changed to auricular fibrillation and later to normal mechanism with inverted P waves and delayed A-V conduction. On the second admission the auricular flutter was again present and vagus experiments were very successful in demonstrating a regular auricular activity with auriculo-ventricular blocking (Fig. 2). After a massive dose of digitalis auricular fibrillation began and persisted. These abnormal auricular

rhythms and mechanisms are associated with auricular muscle changes which in this case resulted from the pressure of the tumor, encroaching on the sinus area. The inverted P waves signify an abnormal course of the impulse through the auricles. The electrocardiographic findings point, therefore, definitely to pathology in the auricular muscle which, as the necropsy showed, was associated directly with a tumor pressing on the auricle and atrophy of the underlying auricular muscle.

In this case it was evident, therefore, as Dr. Dock pointed out, that there was but one possible diagnosis to make and that was tumor. The lack of expansile pulsation or any visible movement at all in the mass and the absence of a tracheal tug, reduplication of the heart sounds and pain ruled out in large measure an aneurism of the aorta. Again, there were no definite symptoms of sufficient gravity to indicate an aneurism of the right ventricle and the absence of symptoms and signs of tricuspid stenosis made a diagnosis of dilatation of the right auricle unjustifiable.

DISCUSSION

Tumors of the heart are not common but do occur in small numbers among the cases of any large clinic. The tumors which may be classed together into this group, as is well known from the literature may arise (1) from the heart itself, (2) from the pericardium, or from the adjacent portions of the great vessels or neighboring tissues of the mediastinum.

Link,[1] in 1909, collected ninety-one cases from the literature which he concluded were primarily of cardiac origin. Meroz,[2] 1912, selected fifty-five cases which he thought had their origin in the heart. Since that time Norton,[3] Gottel [4] and Weltmann [5] have each reported a case of a primary heart tumor.

According to the classification of Meroz the primary tumors of the heart may be (1) valvular; (2) intramuscular, and (3) intracavitary.

The tumor we observed belongs to none of these latter groups but must fall in its clinical aspects among those of the pericardium. It is questionable whether it was attached to the auricle in its earlier period of development. This attachment with the definite deterioration

1. Link, R.: Klinik der primärer Neubildungem des Herzens, Ztschr. f. klin. Med. **57**:272, 1909.
2. Meroz, E.: A Clinical Study of Three Cases of Primary Tumor of the Heart, Internat. Clin. **4**:231, 1917.
3. Norton, W. H.: Myoma of the Heart, Am. J. M. Sc. **158**:689, 1919.
4. Göttel, L.: Ein Fall von primären Herztumor, Deutsch. med. Wchnschr. **45**:937, 1919.
5. Weltmann, O.: Klinschr Beitrag zur Kasuistik primärer Herztumoren, Wien. klin. Wchnschr. **33**:537, 1920.

of the auricular muscle may have occurred in the later stages of the disease. Our tumor was definitely of aortic origin with secondary attachment to the heart.

The tumors decribed arising from the pericardium are (1) fibroma; (2) primary sarcoma; (3) myxoma; (4) parasitic cysts, and (5) dermoids. Fornia[6] recently made a collection of sixteen such cases. Secondary tumor metastases are not uncommon. These may arise from carcinoma, sarcoma, Hodgkins disease or lymphosarcoma situated in adjacent or distant regions of the body. Inflammatory nodules are also seen. Recently one of us [Burrows] observed such a case at necropsy. The nodules in this latter case were multiple. The largest measured about 1cm. in its longest diameter. The whole of the visceral pericardium was thickened. The nodules were striking histologically on account of the large number of foreign body giant cells which they contained. There were also similar inflammatory nodules in the lungs, pancreas, suprarenals and kidneys. The etiology was not determined. Diabetes mellitus was the cause of death.

These various cardiac tumors, as is well known, according to their position may simulate in their clinical picture any one of a great variety of grave cardiac diseases.[2] For this reason up to the time of the development of the roentgen ray their diagnosis was practically impossible, as has been stated by Oppolzer,[7] Gottel and others.

At the present time, as a few recent cases and our case illustrate, this may no longer be true for those tumors presenting on the surface of the heart. The cardiac cachexia not otherwise explained should, therefore, be most carefully studied by these means not only for the importance of improving these diagnostic methods but also from the standpoint of treatment.

The thorax is no longer a barrier to the surgeon. Tuffier[8] recently reported the successful partial removal of a dermoid the size of two fists which was adherent to the aorta and encroached onto the wall of the auricle and ventricle. The clinical symptoms were those of a grave angina pectoris. The case was diagnosed a cyst by Vaques. The tumor was partly calcified and was filled with greasy material. The incision, drainage and disinfection took six months. The patient recovered completely and is now free from the symptoms of angina pectoris and is in good health.

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6. Forni, G.: Primary Tumors of the Pericardium, Tumori **4**:523, 1914.
7. Oppolzer: Quoted by L. Krehl; Diseases of the Myocardium. Nothnagel's Encyclopedia of Practical Medicine. Diseases of the Heart, translated and revised by Dr. George Dock.
8. Tuffier: Tumors Primitives du Coeur. La Chirurgie du Coeur. (Piéce presentée a la Societe de Chirurgie, Paris) 1920.

Our case was brought to the attention of Dr. Evarts A. Graham who considered it an operative possibility had it been seen before the grave cardiac arrhythmias, irregularities and signs of heart failure (the so-called decompensation) had developed.

PATHOLOGY

Pathologically, as stated above, we have been unable to find any counterpart of this tumor in the literature of heart and aortic tumors. Tumors of the aorta are not common. The catalogue of the Surgeon General's Library reports but fifteen papers on this subject. Two of these were written in the eighteenth century before the time of careful histologic study of tissues. Three were cases of secondary carcinomatous metastases. One was a parasitic cyst in a dog, and one other was a blood cyst. Three were primary sarcomas, and one, reported by Threadgill, was a cartilaginous mass in the aorta of a negro child. The paper by Okada was not obtained, and another by Maixner adds nothing new to this subject.

Joel,[9] in 1890, reported the occurrence of a teratoma of the pulmonary artery. As stated above, our tumor is not a neoplasm but it is evidently of inflammatory origin. The pedicle has the structure of an arterial branch of the aorta which has undergone dilatation of its orifice and secondary atheromatous obliteration. The tumor has all the characters of an atheroma of a massive size.

We at first thought that similar tumors might have been observed and confused with dermoids or fibromata of the heart or pericardial tumors. A careful study of the gross and microscopic descriptions of such cases described in the literature has failed, however, to reveal any such similarities. (Morris,[10], Lambert and Knox,[11] Christian [12] and Dangschaat.[13])

Again, there is no evidence that it was primarily an aneurysm. It is more that of a granuloma undergoing secondary changes.

The etiology is obscure. It is impossible to be certain that it is related to other evidences of inflammatory disease of the heart and the aorta in this case and the supposed syphilitic infection. Levaditi

9. Joel, J.: Ein Teratom auf der arteria pulmonis innerhalbs des Herzbeutels, Virchows Arch. f. path. anat. **122**:381, 1890.

10. Morris, R. S.: Dermoid Cysts of the Mediastinum, Med. News **87**:404, 438, 494 and 538, 1905.

11. Lambert, S. W., and Knox, L. C.: Intrathoracic Teratoma, Tr. Assn. Am. Phys. **35**:17, 1920.

12. Christian, H. A.: Dermoid Cysts and Teratomata of the Anterior Mediastinum, J. M. Research, **2**:54, 1902.

13. Dangschaat, B.: Beiträge zur Genese, Pathologie und Diagnose der Dermoid Cysten und Teratom im Mediastinum Anticum. Beitr. z. klin. Chir. **38**:692, 1903.

stains were made of the tumor, of the nodules in the endocardium; of the left ventricle and of the aorta. The poor fixation of the tissue, however, made the negative results of no importance.

Its rarity cannot be accounted for. In this location it might be associated with the rarity of an artery arising from this part of the aorta. This does not explain, however, its absence of occurrence in other regions of the body.

It has been of interest, therefore, for us to report this case as a peculiarly rare clinical entity, the existence of the tumor of which is possible of diagnosis and which must fall, therefore, within the domain of the surgical treatment of the present and the future.

BACILLUS ACIDOPHILUS AND ITS THERAPEUTIC APPLICATION

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NEW HAVEN, CONN.

Bacillus acidophilus was first observed and described in 1900 by Moro.[1] It is a rather large gram-positive bacterium which is quite pleomorphic and which in many respects resembles Massol's *Bacillus bulgaricus* and Tissier's *Bacillus bifidus*. It was claimed by Moro to be the chief inhabitant of the intestine of infants that subsist entirely on mother's milk. This assertion was disputed by Tissier[2] who protested that *B. bifidus* holds the place of prime importance. *B. acidophilus* and *B. bifidus* are now known to constitute the main flora of the breast-fed child, the latter being, perhaps, the more prominent of the two. As the diet changes and becomes more and more complex, there is a corresponding change in the kinds and relative numbers of intestinal bacteria, until finally the intestinal population assumes the character of that of the ordinary adult. *B. acidophilus and B. bifidus* gradually disappear to such an extent that their presence can be demonstrated in the feces with considerable difficulty only. Their place has been taken by various other organisms, some of which are decidedly fermentative and putrefactive, and, according to Metchnikoff and others, assume a rôle harmful to the host.

B. acidophilus is practically indistinguishable from *B. bulgaricus* and has undoubtedly often been mistaken for the latter. There are, however, two well-known points of distinction between these two organisms. *B. acidophilus* produces relatively little acid in milk (less than 1 per cent.) even after continued incubation, whereas *B. bulgaricus* may produce as much as 3 per cent. Furthermore, *B. acidophilus* attacks maltose with acid formation, while *B. bulgaricus* has no action on this sugar. The most important mark of difference is that relating to intestinal implantation. *B. bulgaricus*, as numerous experiments have shown, is unable to live and multiply in the intestine of the white rat and of man, whereas *B. acidophilus* undergoes rapid development when administered by mouth, or as the result of milk, lactose or dextrin feeding.

Rettger and Horton[3] and Hull and Rettger[4] had shown that the feeding of milk or lactose to experiment animals, including the white

1. Moro, E.: Ueber den *Bacillus acidophilus*, Jahrb. f. Kinderh. **52**:38, 1900.
2. Tissier, H.: Réchérches sur la flore intestinale normale et pathologique du nourisson, Thése, Paris, 1900.
3. Rettger, L. F., and Horton, G. D.: A Comparative Study of the Intestinal Flora of White Rats Kept on Experimental and on Ordinary Mixed Diets, Centralbl. f. Bakteriol. **73**:362, 1914.
4. Hull, T. H., and Rettger, L. F.: The Influence of Milk and Carbohydrate Feeding on the Character of the Intestinal Flora, J. Bacteriol. **2**:47, 1917.

rat, tended to decrease the number of ordinary intestinal bacteria and to establish an organism of the *B. acidophilus* type. Hull and Rettger [4] demonstrated that an almost complete acidophilus flora may be obtained in the albino rat by the daily feeding of 2 gm. lactose. Cheplin and Rettger [5] confirmed these observations on white rats, and showed further that similar results may be had in man. They found that the daily ingestion of from 300 to 400 gm. lactose brought about a very profound change of bacterial types in which *B. acidophilus* greatly predominated, often to the extent of at least 90 per cent. of the viable organisms present. Torrey [6] had shown that in the treatment of typhoid fever patients with lactose from 250 to 300 gm. were necessary daily in order to establish an acidophilus flora.

It was not until the spring of 1919 that any serious attempts were made to administer cultures of *B. acidophilus* for the purpose of bringing about an implantation and proliferation of this organism in the intestine. Cheplin and Rettger [5] demonstrated that transformation of the flora may be brought about easily and within the course of four to six days in apparently normal human subjects by the daily administration of 300 c.c. pure whey-broth cultures of the organism. *B. acidophilus* was often present in the feces to the extent of from 85 to 90 per cent. of the cultivable bacteria. Similar results were obtained with all of these subjects when 150 c.c. of the culture and 150 gm. milk sugar were given in place of the requisite amount of culture alone.

Implantation of *B. acidophilus* may be brought about, therefore, by any one of the three methods just described. In fact, the results, as measured by the bacterial picture, were practically the same in each method, as is clearly shown in the curves and tables published at some length in book form.[7] The whey-broth culture was soon displaced, however, by the acidophilus milk culture which was devised by us early in 1920. On account of the extreme importance attached to the use of *Bacillus acidophilus* milk the following brief description is given of this product and of the method of preparation.

BACILLUS ACIDOPHILUS MILK

Fresh skimmed cow's milk is sterilized in one heating at 115-120 C., the time required being determined by the volume of the milk and the nature of the container. Quart lots in ordinary glass flasks are heated

5. Cheplin, H. A., and Rettger, L. F.: Implantation of *Bacillus acidophilus*. Proc. Nat. Acad. Sc. **6**:423, 704, 1920; Proc. Soc. Exper. Biol. & Med. **17**:192, 1920; **18**:30, 1921.

6. Torry, J. C.: The Fecal Flora of Typhoid and Its Reaction to Various Diets, J. Infect. Dis. **16**:72, 1915.

7. Rettger, L. F., and Cheplin, H. A.: A Treatise on the Transformation of the Intestinal Flora with Special Reference to the Implantation of *Bacillus acidophilus*, Yale University Press, 1921.

22-24 minutes. Properly heated milk should have a dark cream color, but should not be distinctly browned. After cooling to at least 37 C. the milk is inoculated with pure strains of *B. acidophilus* which have been grown, by repeated transfers, sufficiently long in milk to develop rapidly and bring about coagulation of the casein within twenty-four hours at a temperature of from 35 to 37 C. Viable milk cultures of the organism are employed as the inoculum, and at least 10 c.c. of the inoculum are transferred for each liter of milk treated. After thorough mixing, the newly inoculated milk is incubated for the period stated.

At the completion of the full incubation period the casein appears as a soft curd, with a thin layer of clear or almost clear whey over the surface. On thorough shaking the curd falls to pieces and the milk acquires a smooth consistency which resembles that of thick cream. Even during long standing there is no marked separation of whey from the curd, or collection of the curd into granules or lumps. The acidity of the acidophilus milk is never high, as compared with that of *B. bulgaricus* milk, seldom reaching more than 1 per cent., even after a week's incubation at ordinary room temperature. The odor and flavor resemble to some extent those of a high grade buttermilk and should be agreeable to persons who do not have a dislike for sour-milk products as such. The odor and taste are, however, decidedly characteristic, when the milk culture is pure. Contaminating organisms, if they have developed appreciably in the milk, owing to imperfect sterilization or subsequent contamination, change the character of the milk in such a manner as to be recognized readily by the odor and taste, and often by the physical appearance of the product. For example, the ordinary milk souring bacteria cause the usual sour milk fermentation and coagulation, and the common spore forming organisms of the *B. subtilis* type produce offensive products characteristic of the group. These are the main types of contaminants thus far encountered in the acidophilus milk by us.

THERAPEUTIC APPLICATION OF BACILLUS ACIDOPHILUS

In the first series of experiments with man, seventeen different subjects were employed. Fifteen were apparently normal and two had a long history of intestinal disturbances. Most of the subjects served in more than one experiment, bringing the total number of individuals up to forty-three. The entire work involved the bacteriologic examination of 580 stools. Implantation of *B. acidophilus*, with the predominance of this organism to the extent of at least 80 per cent. of the total flora of the feces, was brought about almost at will. Particular attention is called to the fact, however, that no two subjects required the same minimum amount of lactose, *B. acidophilus* culture or combina-

tion of the two, to yield to the transforming influence within a given period of time.

In all of the experiments the change in the intestinal flora was determined by the three following bacteriologic methods: (1) Plating of fecal suspensions (in physiologic sodium chlorid solution) in whey agar and the numerical study of *B. acidophilus*-like colonies; (2) preparation of deep whey-agar (Veillon) tubes for the determination of gas producing organisms of both the aerobic and anaerobic types; and (3) staining of slides by the Gram method and a differential study of bacterial types. These methods proved to be most valuable, and were employed also in the more recent work on intestinal flora in abnormal subjects. For a full description of these and all other methods employed in the earlier investigation, and for a full account of the results, the reader is referred to our monograph [7] on intestinal flora.

No difficulty was experienced in obtaining the cooperation of practicing physicians in our investigation of the therapeutic properties of *B. acidophilus* when administered by mouth, either alone as a pure milk culture or in combination with different amounts of lactose. It became apparent at the outset that the acidophilus milk is much to be preferred to the lactose broth or whey broth cultures of the organism for the following reasons: The milk is tolerated even by those who are unable to retain the simplest and most wholesome foods for convalescents; when properly prepared and preserved the acidophilus milk remains practically unchanged, and free from bacterial contamination and deterioration: it contains at least 4 per cent. lactose which in itself serves to stimulate *B. acidophilus* proliferation in the intestine; it is nutritious, and for those who cannot take or do not tolerate other foods it does much toward the maintenance of nitrogen balance and the prevention of tissue waste, when taken in the usual amounts, from 1 pint to 1 quart daily and finally, as a young culture of viable bacteria it is particularly potent in bringing about the desired transformation of bacterial types in the intestine.

PATHOLOGIC CASES

It is not our purpose here to present a detailed history of the individual cases, nor to dwell at any length on the treatment and the bacteriologic results. A full account of these studies will be published, however, at an early date. The subjects under observation may be subdivided into the following groups; (1) Chronic constipation with the symptoms of so-called autointoxication and other accompanying pathologic conditions, some of them acute, 20 cases; (2) chronic diarrhea following an attack of bacillary dysentery, 2 cases; (3) colitis.

at times bloody, and more or less mucous, 3 cases; (4) sprue, 2 cases; (5) dermatitis (eczema), 3 cases.

These thirty cases are exclusive of those which have come under our observation within the past few weeks. Nor do they include those which are being studied and treated in other institutions through our cooperation. Particular attention is directed to only a few of these thirty cases.

The subjects were requested to bring to the laboratory one or two specimens of stool before taking the acidophilus treatment, and for a while daily samples, when procurable, after the first administration of the acidophilus milk or of the milk plus stated amounts of lactose. Bacteriologic examinations were made of these specimens, and their results correlated with the clinical findings. It was the aim to obtain a pronounced transformation of the bacterial flora of the intestine in the shortest period of time; hence, so-called "maximum" treatment was given from the start. As lactose has a marked laxative effect when taken internally in sufficient amount, persons having a history of obstinate chronic constipation at first usually received 1 quart of the acidophilus milk plus 100 gm. lactose daily. The powdered lactose was added to the acidophilus milk in the flask and the contents thoroughly shaken. Subjects were instructed to take the daily supply in three equal portions, one in the forenoon, another in the afternoon, and the third immediately before retiring for the night, and in every instance at least two hours before and after meals. There were no regulations as to diet, except that the subjects were urged to refrain from the use of food which by experience or training they knew to prove injurious.

If, in the course of three or four days constipation was not relieved except by an enema, which was advised when the condition of the subject made it absolutely necessary, the daily amount of lactose was increased by 25 or 50 gm. On the other hand, when stimulation of peristalsis became too marked and a diarrheal condition resulted from the taking of the full amount (1 liter of acidophilus milk and 100 gm. lactose), the quantity of lactose was reduced by 25 or 50 gm. In a few instances the volume of milk taken daily was reduced to 500 c.c., with or without a reduction in the amount of lactose.

In the diarrheal cases (including colitis and sprue) the treatment consisted in the daily administration of 1000 c.c. acidophilus milk without any added milk sugar. The milk was easily tolerated by the patients; in one instance, however, the volume was reduced after the first few days to 500 c.c. owing to a feeling of fulness and partial loss of appetite of which the subject complained. Persons who could

not take other food in any form retained the acidophilus milk and complained of no distressing or otherwise injurous effect.

Chronic Constipation.—The two following cases of chronic constipation are briefly reviewed here, as they happened to be the first to take the treatment, and were among the most obstinate advanced cases of alimentary toxemia that have as yet come under our observation.

Case 1.—Subject D. had suffered from constipation for at least seven or eight years, and complained of fulness of the abdomen and of gas and pain in the epigastric region, also of an almost constant headache, visual disturbance, general discomfort after meals, loss of energy and initiative, general malaise, and what was most disturbing to him, melancholia and other indications of lessened mentality. He regularly required unusually large doses of laxative to induce bowel evacuation, and stated that he had been absolutely dependent on cathartics for at least two years for relief which was even then only partial and of very short duration.

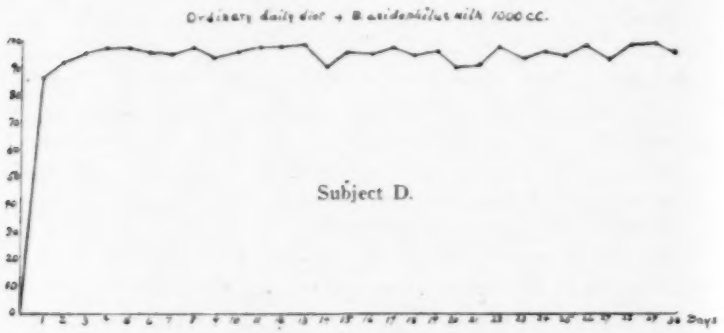

Fig. 1.—Results of addition of *B. acidophilus* milk to diet.

The subject was given 1 liter acidophilus milk daily, and instructed, as were all others, not to employ a cathartic, and to bring daily specimens (when possible) of stool. He reported almost daily at the laboratory for observation. Unfortunately, no sample of stool could be obtained before the beginning of the treatment. However, in none of the numerous experiments already conducted on man was *B. acidophilus* observed in the feces before treatment with *B. acidophilus* culture or special carbohydrates without much difficulty and then only rarely and in very small numbers; hence, it is safe to assume that in cases of constipation at least the per cent. of cultivable *B. acidophilus* cells is, without special stimulation, at or near 0.

Within forty-eight hours after the first ingestion of the milk culture the bacteriologic examination of the feces revealed a marked transformation of the flora with a preponderance of *B. acidophilus*-like organisms. By the end of the fourth day the gas producing organisms had apparently completely disappeared from the intestine, and the aciduric type reached a percentage level of at least 90 which it maintained throughout the course of the treatment (Fig. 1). The administration of the acidophilus milk had to be discontinued and the experiment ended after a period of thirty days, owing to the seasonal closing of the laboratory. The subject left very soon after for continued residence in the Orient.

On the third day after the subject began the treatment he reported a normal bowel evacuation, and continued to report at least one daily movement, barring one exception, for the remainder of the experimental period. There was an apparent change within the first three days in the patient's general condition. By the end of the first week he reported complete relief from gaseous distension and pain in the epigastic region. His appetite was good, and he was free from the usual intestinal disturbance following a substantial meal. Little by little he indulged his appetite more and ate heartily of meats, biscuits and pastries with apparent impunity, which hitherto he was forced to avoid. His headaches and mental disturbances disappeared, and he resumed his full daily duties with, as he stated repeatedly, new strength and endurance. These claims were fully borne out by his appearance and actions.

CASE 2.—Subject W. was an almost exact duplicate of D. He had, however, marked dilatation of the descending colon. He received essentially the same treatment as Subject D., and though he responded more slowly at the beginning, the bacterial transformation was almost complete by the end of the first week, and the percentage of *B. acidophilus* remained at 85 to 95 throughout the course of observation. Gas-forming organisms disappeared early. On the third day after the first administration of the acidophilus milk he presented a natural specimen of stool which appeared normal, and thereafter, with very few exceptions, reported daily normal evacuations. His physical and mental condition had been such as to cause him considerable alarm. He had over a period of five or six years consulted several specialists and had been advised by two of them to undergo an operation for the colon dilatation.

This subject's general condition began to improve almost immediately. He reported constant improvement from day to day, which was apparent also in his facial expression and in his actions. He was under observation for eight months. After about three months of the treatment he was advised to take the milk less frequently and to continue its gradual elimination from the diet for the purpose of determining whether it could not be dispensed with eventually. Until early in May, and for a period of four weeks, he took only 1 or 2 quarts a week. During the succeeding six weeks he called twice for the acidophilus milk, stating each time that, while he still continued to be in very good condition, he thought it desirable to take a pint or a quart because of slight premonitions of returning trouble. He has not reported in person since, and in so far as the writers know there has been no recurrence.

Contrary to the rule, both these subjects responded readily to the use of the acidophilus milk, without any added lactose. Two other subjects have reacted similarly. On the other hand, most of the chronic constipation cases required 100 gm. added milk sugar, and one of them required as much as 200 gm. daily along with the quart of acidophilus milk. In no instance was there a failure to bring about relief when the treatment was not interrupted early.

Chronic Diarrhea.—CASE 3.—Subject B. A Bohemian, male, 42 years old, residing in New Haven since April, 1921. He was seized in September, 1907, with an attack of acute diarrhea accompanied with tenesmus. The stools were bloody and contained mucus. Temporary recovery; no bacteriologic examination; recurrence in the spring of 1908; in hospital at Frankfurt a. M. for six weeks. Bacteriologic examination negative. In sanitarium at Meran in Tyrol. Limited diet; temporary recovery. Recurrence in summer of 1908. Diarrheal condition more or less constant till 1914, when *B. dysenteriae* was identified in the stools. Temporary recovery. Recurrence in January, 1915, while living in Silesia. In dysentery hospital six months. Shiga-Kruse bacillus again isolated from feces. Serum treatment. Left hospital as incurable. In 1915 in hospital in Hamburg; for six months exclusive diet of oatmeal gruel. Treat-

ment resulted in temporary cure. Normal formed stools for the first time since 1909. Recurrence after four weeks; acute abdominal pain and diarrhea. Feces examination negative. Condition much improved after four months' residence in Norway. Partial recurrence in England (December, 1920, to April, 1921). Took ship for America April 2, 1921. Apparently normal on ship and for a few days after arrival in New Haven.

Within a week after subject B. reached New Haven he was suddenly seized with an attack of profuse diarrhea and acute pains in the descending colon. Presented himself for treatment in April. Stools were watery, very dark, and of pronounced putrefactive odor. By the third day the stools appeared lighter (yellowish) in color and less watery. After one week's treatment the abdominal pains had practically disappeared, the feces rapidly approached the normal and the diarrheal condition had almost completely ceased. During the second week's treatment he pronounced himself fully recovered. He continued apparently normal for about three weeks when owing to dietary indiscretion there was a slight return of the disturbance. The night before the partial recurrence he attended a banquet and indulged freely in all that was set before him, including two courses of meat. This setback lasted only two or three days.

Subject B took one quart of acidophilus milk daily from the first without any intermission. Except for the above mentioned and a second slight recurrence early in June brought on apparently by bathing in cold sea water, he was, according to all appearances and his own claims, in normal condition for two months and to the time when the experiment was interrupted owing to the closing of the laboratory (July 1). The subject has on several occasions since then informed the writers that he has suffered no recurrence.

Another subject whose case in some respects was similar to this reacted favorably to the treatment. A full history of this case, with results, will be given in a later paper.

Colitis.—The two cases of colitis which came under our observation were of the acute type. One was apparently uncomplicated, but had a long history of intestinal disturbance. The other was complicated with nephritis. The former responded completely to the milk treatment (800 c. c. daily) and after about one month returned to his work. He continued in apparently good health for about two months when he experienced a partial reversion, due to overconfidence in his improved condition and indulgence in late shore dinners.

The second patient gave every indication of physical improvement when, owing to his serious nephritic condition, he required special hospital treatment and was compelled to discontinue the use of the acidophilus milk. His severe abdominal pains had almost completely disappeared, however, and he was suffering apparently very little from the colitis.

Both of these cases will be presented more fully at a later date.

Sprue.—Case 4.—Subject Wr had contracted sprue while in China. Though the affection was not of an acute type, it was serious and compelled him to return to the United States where for at least two years he was constantly under its annoying and debilitating influence. He took one quart of the acidophilus milk daily for six weeks during which time the character of the feces changed completely from the clay-colored, soft and extremely offensive type to the yellow, almost formed and almost odorless. The gas disappeared from the colon, and the subject stated from day to day that he thought he

was for the time at least in perfectly normal condition. The bacteriological results of fecal examination are shown in Figure 2.

A second case of sprue was that of a returned missionary who had contracted the disease during twenty years of service in China. When seen by the senior author he had been confined to his bed for several months with the characteristic symptoms in their most acute form, including tetany. He was emaciated and subject to abdominal pains and gaseous distension.

This patient has been under observation for almost six months, during which period he has taken, with very few brief intermissions, one quart of acidophilus milk daily (the milk being sent to him by special messenger). He has shown from almost the beginning gradual improvement in his condition, though he has from time to time suffered relapses.

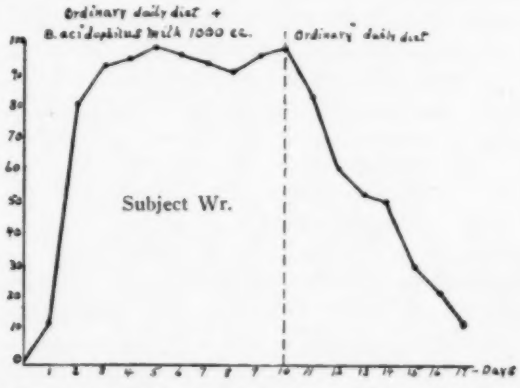

Fig. 2.—Results of addition of *B. acidophilus* milk to ordinary diet and then returning to ordinary diet.

Dermatitis.—All of the three cases of dermatitis were those of eczema. Treatment of two of them was discontinued before any definite results could be obtained. The third patient (Subject Q) responded completely to the treatment, and for five months has been free from the eczema which for at least twelve years had been a source of constant annoyance and embarrassment. When first seen practically the entire face was involved, as well as other parts of the body.

Transformation of the intestinal flora was effected with considerable difficulty, and required fully a month. However, by increasing the daily amount of added lactose from 50 to 100 gm. a high aciduric flora was established and maintained throughout the remainder of the experiment. Concomitant with this change there began a clearing of the skin which continued until after another month almost all traces

of the dermatitis had vanished. At the present time there are no indications of a return of the affection.

GENERAL COMMENTS ON THE THERAPEUTIC APPLICATION OF BACILLUS ACIDOPHILUS

The work of the past two years has shown conclusively that *B. acidophilus* can be implanted in the intestine of man almost at will, and that its colonization there may be such as to displace at least 80 per cent. of the usual mixed flora. This transformation is brought about by the administration of at least minimum amounts of lactose or of living acidophilus culture or of a combination of both. The most practical and effective method is by means of the acidophilus milk or of the milk plus definite amounts of lactose given daily. Cases of obstinate constipation almost invariably require some added lactose.

B. acidophilus is, according to all available information, an organism which does not elaborate toxic or other harmful products. It is classed as a strictly nonfermentative and nonputrefactive micro-organism. It is present in the intestine of nursing infants in relatively large numbers, and at all times is an inhabitant of the intestine of children of all ages and of the adult. It is demonstrated with difficulty, however, in the feces of persons subsisting on the usual mixed diet of which protein forms a large part, owing to its being suppressed by the other intestinal micro-organisms which flourish on the usual mixed diet. Administration of sufficient lactose (or dextrin) stimulates the proliferation of the relatively few aciduric bacilli. Ordinary milk accomplishes the same result, but enormous amounts of the milk are usually required to bring about the change. Pure viable cultures of *B. acidophilus* accomplish the same thing, with or without added lactose, but when applied alone definite minimum quantities of the cultures or suspensions, which must be determined for each individual, are necessary.

Viable cultures of *B. acidophilus* when used in sufficient amounts and under the right conditions have important therapeutic properties. They are of particular merit in the treatment of chronic constipation and of diarrheas, as the numerous experiments thus far conducted by the writers conclusively show. Furthermore, *B. acidophilus* should be of marked benefit in the treatment of other ailments which are directly or indirectly referable to disturbed function of the digestive system and of the chief organ of elimination; the results already obtained on several individuals bear out this promise.

A word of warning should be sounded at this time. The principle on which the acidophilus treatment is based has been clearly set forth in the various publications from this laboratory. It is only when these principles are adhered to that favorable results are to be expected.

In the first place, this is not a cure for all kinds of ailment, nor will all cases of disturbances falling within its category necessarily respond to the acidophilus treatment. In the second place, it is not an elixir in the sense that Metchnikoff's *B. bulgaricus* was for a while supposed to be. The ingestion of relatively few acidophilus bacilli will not lead to implantation and bodily improvement. A minimum amount of bacterial culture is necessary to bring about these results, and for this reason the writers have adopted the acidophilus milk culture as the surest and most effective means of attaining the desired results. So-called acidophilus tablets and powders can be of no use whatever in effecting transformation of flora and relief from trouble, either when taken as such or when used for the production of acidophilus milk. As has been fully pointed out elsewhere, the preparation of viable and satisfactory acidophilus cultures is impossible without the absolute sterilization of the medium to be used, and without the aseptic use of pure cultures of the organism as inoculum.

The fullest benefit from the acidophilus treatment can be derived only when the patient is under practically daily observation and when thorough bacteriologic examinations of the feces are made at frequent intervals. These examinations are of extreme importance in determining the amount of acidophilus milk or milk and lactose that are to be taken from day to day. Unless at least a reasonable degree of transformation of the intestinal flora to the aciduric type is effected little should be expected from the clinical standpoint. In any application of the principle of acidophilus treatment immediate results must not always be expected. In a number of instances in which the treatment became effective we have failed to obtain a favorable reaction until after one to two weeks' application, and in certain few cases there was no favorable response until a month after the initial administration of the acidophilus milk or the milk and lactose. This is to be expected when the results to be sought must of necessity be indirect, as in the positive eczema case. Yet, such cases may clear up and in the end prove to be some of the most satisfactory.

Various plans are now being considered for making *B. acidophilus* milk generally available and under such conditions as to assure its viability and purity.

THE EFFLUX OF BLOOD FROM THE CAROTID ARTERY OF THE DOG AND ITS EXPRESSION BY A GENERAL EMPIRICAL FORMULA *

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The study of the normal and pathologic significance of the blood pressure has been a subject of interest for many years. It was not until mechanical instruments were available, however, that any accurate measurements of blood pressure were taken. Ludwig, in 1847, first obtained a blood pressure tracing. In 1882, almost forty years later, V. Basch invented the tonometer. Roy and Adami in 1890 modified this for external use and Riva Rocca in 1896 manufactured the first practical clinical instrument for taking blood pressures.

During the last two decades, the clinical literature has been filled with blood pressure observations on both man and animal. The normal blood pressure of man has been established by a score of investigators; Alvarez,[1] Barach and Marks,[2] Cook,[3] Dawson,[4] Fisher,[5] Frau Wolfensohn-Kriss,[6] Goepp,[7] Greene,[8] Kammerer,[9] Lee,[10] MacKenzie,[11] Michael,[12] Sallom,[13] Smith,[14] Sorapure,[15] Weysse,[16] and Woley.[17] The

* From the Physiology Department, University of Minnesota.

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series by Goepp included 9,996 determinations; that of Fisher, 12,647; and that of MacKenzie, 31,934. A recognized normal blood pressure has been established also by several large insurance companies. The Northwestern National Life Insurance Company, for instance, uses an average scale ranging between 120 systolic pressure at 20 years to 136 systolic at 60 years. Much has been done to correlate high blood pressures with certain diseases, for instance, the toxemias of pregnancy, hypertension and arteriosclerosis.

Although blood pressure has been studied extensively, no attempt has been made to establish a correlation between it and blood flow. The present work is an effort to secure such a correlation. By means of quantitative methods and the graphic analysis of the results, a relationship between the arterial blood pressure and the efflux of blood from a cannula of known size was obtained. The data of this work are entirely from dog experiments. Any application of this relationship to direct arteriovenous transfusion can be used only after further observations on human material are made. This work was done under the physiology department at the University of Minnesota and material assistance was rendered by Dr. F. H. Scott and Dr. R. E. Scammon. Credit is also due to Mr. J. F. Borg and Mr. H. R. Smithies, who assisted in some of the experiments.

In addition to obtaining the relationship of blood pressure to blood flow, the total blood volume of each dog was determined. These data are reserved for a later publication.

MATERIAL

The dog was selected as the best laboratory animal to be used for the experiment. Eighteen dogs were used, differing in sex, variety, and size. No distinction was made between sex and variety since these factors did not bear on the problem. The size of the animal was important, however, since it was necessary for the carotid artery of the dog to be larger than the lumen of the cannula used for the experiment. The dogs were all in good health and had not been used for previous experimentation of any kind. The cannules used for the problem were manufactured by the Wilson and Wilson Company, Boston. These cannules are made from the same material as are their nickle plated steel needles and they correspond to them in gage size. The ends of the cannules are made blunt, however, to eliminate experimental error.

METHODS

A uniform technic was employed for all of the experiments. From twenty to thirty beakers were prepared for the collection of the blood of the animal. Into each of these 5 c. c. of sodium citrate solution were

measured by means of a buret. A bulb, T-shaped cannula was inserted into the left carotid artery and one arm connected to a mercury manometer for recording arterial blood pressure.

The internal surface of the metal cannula was coated with liquid petrolatum to prevent the formation of a blood clot. All but a thin film of the petrolatum was washed out by hot water. A rubber tube was fastened to the cannula in order to convey the blood from the carotid artery to the beakers. This tube was filled with a solution of physiologic sodium chlorid solution so that the blood flow for the first ten seconds would not be inaccurate. After finishing all the preliminary preparations the last thing done before starting the experiment was to insert this cannula in the right carotid artery. The kymograph was started and a normal curve of blood pressure was taken. Then the clip was removed from the right carotid and the blood was permitted to flow through the cannula. At the end of each ten seconds the blood flow was deviated to another beaker and the time was indicated on the kymograph tracing. When the animal ceased to bleed the arteries were cut and all of the blood was drained from them. No attempt was made to perfuse the animal. The amount of blood in each beaker was accurately measured to 0.5 c. c. The mean blood pressure for the respective intervals of ten seconds was obtained from the tracings. The determinations for all the data necessary in the experiment were now complete, except for the estimation of the area of the cannula lumen. The diameter of the lumen of the cannula was measured by means of a vernier caliper, accurate to one hundredth millimeter. The cross section area of the lumen was calculated by using the formula for the area of a circle: Area=3.1416 (r^2) in which r is the radius in mm.

ACCURACY OF THE DATA

It is essential to estimate the accuracy of the data in order to obtain a relationship between the three variables, blood pressure, blood flow and the size of the lumen of a cannula. The cross section area of the lumen of the cannula can be determined with considerable exactness. All the cannules were measured in the same manner. The diameter of each was obtained by averaging thirty readings of the vernier caliper. By this means an accurate determination of the cross section area of the cannula was obtained. The blood flow per ten seconds is also an accurate measurement since it is not distorted in any way by experimental error. The blood pressure, however, is not as exact an observation. The necessity for an absolutely accurate baseline was not obvious while the experiments were being carried out. The error in its determination occurred because the third arm of the three way cannula was not kept horizontal to the carotid artery. The variation ranged from 2 to 10 mm. Hg.

TREATMENT OF THE DATA

The accuracy of the data is very important for the successful interpretation of the physiologic relationship between the blood pressure and the blood flow. The significance of the results, however, can be obtained only by an application of graphic and mathematical analysis to the data. The methods used in this series of experiments are three in number: (1) the construction of field graphs and drawing curves by inspection; (2) the determination of a general empirical formula, and (3) the comparison of the inspected absolute curves to the respective curves derived by the general empirical formula.

1. The construction of field graphs, together with the establishment of curves showing the central tendency of the data, was the first method of graphic analysis which was attempted. Each graph (Figs. 1, 2, 3, 4, 5 and 6) includes the data which were obtained by the use of a certain cannula. In each figure the abscissa represents blood flow in c. c. per ten seconds, while the ordinate is the blood pressure of the animal in mm. of Hg. The curve drawn by inspection does not signify a curve of mathematical accuracy but merely represents the best expression of the judgment of the author as to the central tendency of the data.

Figure 8 is also a field graph. In this instance the abscissa represents the area of the lumen of the cannula. The ordinate shows the average blood flow per ten second interval for the respective cannules.

2. After the field graphs were made and the inspected curves were drawn for each, a general formula was calculated expressing the blood flow in terms of the blood pressure and the cross section area of the cannula. This general formula was obtained by the method of trial and error. In determining the equation, the values of the cross section area of the cannula were kept unchanged. Blood pressure values were also kept as nearly similar to the respective observed determinations as the nature of the data would permit. The best general formula can be expressed as follows: Blood flow (c. c.)=0.17 (area [sq. mm.]) (Blood pressure [mm. Hg.]) in which blood flow is the efflux of blood from a cannula per ten seconds of time, area is the cross section area of the lumen of the cannula in sq. mm., blood pressure is the average blood pressure in mm. of Hg., and the number 0.17 is an empirically determined constant.

3. The comparison of the absolute values of the curves drawn by inspection with the corresponding determinations of the general formula is demonstrated graphically and numerically. On each absolute graph (Figs. 1, 2, 3, 4, 5 and 6) both the inspected and the calculated curve are inserted, the former by a solid line and the latter by a broken line.

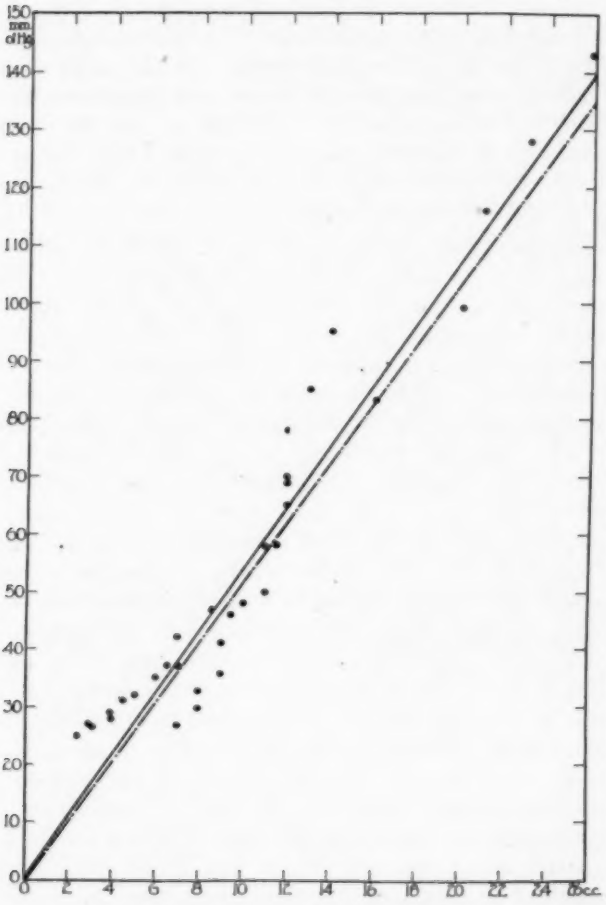

Fig. 1.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had outlet 1.131 sq. mm. in area. Abscissa: efflux of blood in cubic centimeters per 10 seconds of time. Ordinate: blood pressure in millimeters of Hg. Individual cases are indicated by solid dots (for Experiment 1) and by circle-crosses (for Experiment 2). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.) = 0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

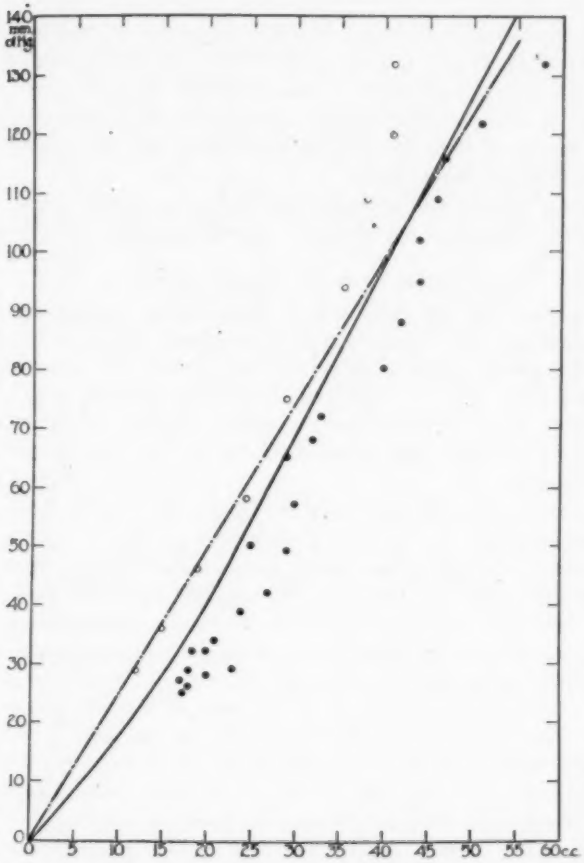

Fig. 2.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had an outlet 2.378 sq. mm. in area. Abscissa: efflux of blood in c. c. per 10 seconds of time. Ordinate: blood pressure in mm. Hg. Individual cases are indicated by solid dots (for Experiment 3), by circle-crosses (for Experiment 4) and by open circles (for Experiment 5). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.) = 0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

In Figure 7 these curves are grouped to a uniform scale. The curves drawn by inspection are paired with those which were calculated and the corresponding pairs numbered according to the respective graphs.

The numerical comparison of the respective values which are taken from the curves drawn by inspection and those calculated by the general empirical formula is seen in Tables 1 and 2.

Table 1 contrasts in parallel columns the observed and the calculated values of both the average blood flow and the average blood pressure for each experiment.

Table 2 shows the observed and the theoretical values of the average blood flow and the average blood pressure for each graph.

EXPERIMENTAL OBSERVATIONS

A summary of the observations made on the data is divided for convenience into four subdivisions: (1) a consideration of the absolute data which are presented by means of field graphs and tables; (2) an enumeration of averages obtained from this absolute data; (3) a comparison of the observed and calculated values, and (4) the significance of the relationship between the blood flow and the size of the cannula outlet.

1. The absolute data available for this study are set forth in the field graphs (Figs. 1, 2, 3, 4, 5 and 6) and in Table 1.

Figure 1 is a field graph based on two experiments. Each of the dogs selected weighed 4.54 kg. The cannula used was gage 16 and had an opening 1.131 sq. mm. in area. The curve, drawn by inspection, shows that 26 c. c. of blood flows from the cannula in ten seconds when the blood pressure is 140 mm. of Hg. This amount of blood outflow steadily decreases until at 25 mm. of arterial pressure only 3 c. c. of blood flows from the cannula per ten seconds of time. The curve indicated by dashes is the general empirical formula: Blood flow (c. c.)=0.17 (area [sq. mm.]) (Blood pressure [mm. Hg.]). It is slightly lower than the curve drawn by inspection.

Figure 2 is a field graph based on three experiments, the dogs weighing 5.67, 13.4 and 7.72 kg., respectively. The cannula used in these experiments was gage 14 in size and had a cross section area of 2.378 sq. mm. The curve drawn by inspection shows that 55 c. c. of blood leave the cannula in ten seconds when the blood pressure is 140 mm. of Hg. The arterial pressure descends rapidly to 40 mm. at which point the efflux of blood in ten seconds is 20 c. c. The curve drawn by calculation from the general formula is a straight line which falls slightly below the inspected curve at a blood pressure above 100 mm. of Hg. and slightly above the inspected curve at an arterial pressure below 100 mm. of Hg.

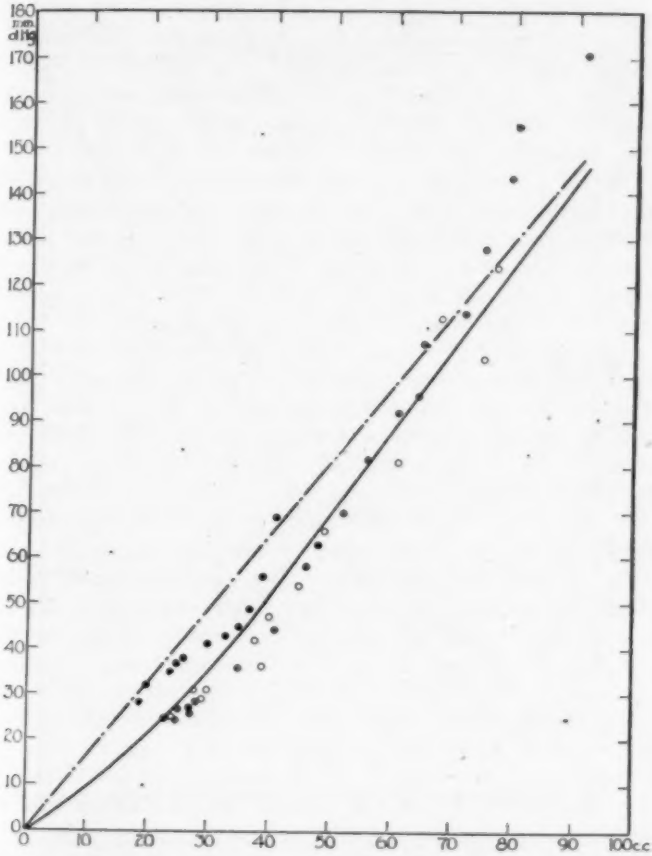

Fig. 3.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had an outlet 3.597 sq. mm. in area. Abscissa: efflux of blood in c.c. per 10 seconds of time. Ordinate: blood pressure in mm. of Hg. Individual cases are indicated by solid dots (for Experiment 6), by circle-crosses (for Experiment 7) and by open circles (for Experiment 8). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.)=0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

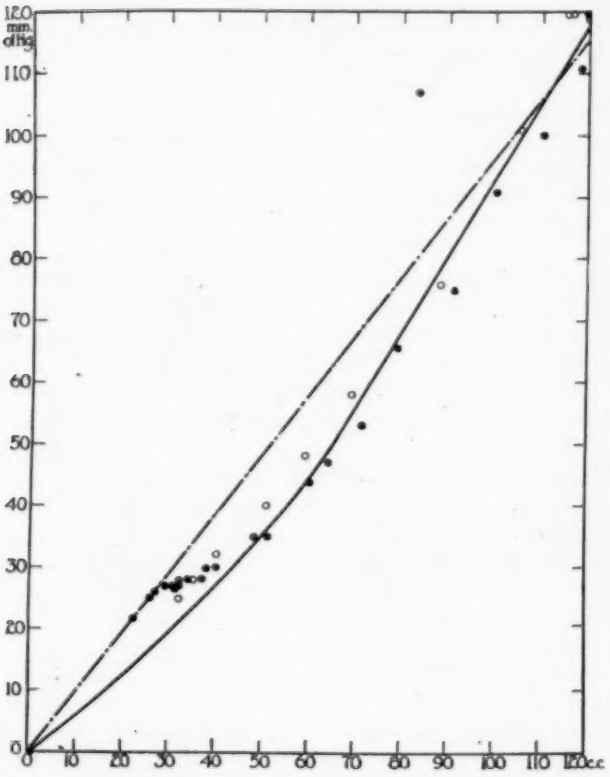

Fig. 4.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had an outlet 5.2 sq. mm. in area. Abscissa: efflux of blood in c.c. per 10 seconds of time. Ordinate: blood pressure in mm. of Hg. Individual cases are indicated by solid dots (for Experiment 9), by circle-crosses (for Experiment 10) and by open circles (for Experiment 11). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.) = 0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

Figure 3 expresses the absolute relationship between blood pressure and blood outflow per interval of time when the cannula has a cross section area of 3.597 sq. mm. Three experiments were carried out to establish this relationship, the dogs weighing 9.54, 20.45 and 15.2 kg., respectively. The blood pressure decreases more rapidly in amount than does the blood flow per unit of time. At 127 mm. of arterial pressure there is approximately 80 c. c. of blood flow from the carotid in ten seconds. The blood pressure decreases rapidly to 25 mm. and the blood flow to 23 c. c. per ten seconds. The calculated curve is at all times higher than the curve drawn by inspection.

The absolute data set forth in Figure 4 varies more widely from the empirical formula than do those of any other field graph. Three dogs, weighing 28.1, 10.13 and 21.8 kg., respectively, were used to establish this relationship. The cross section area of the cannula was 6.07 sq. mm. The inspected curve is distinctly concave descending rapidly from a blood pressure of 118 mm. of Hg. and a blood outflow of 120 c. c. per ten seconds of time to a blood pressure of 50 mm. of Hg. and a blood outflow of 68 c. c. per ten seconds. The descent is then more slow until the efflux of blood per ten seconds of time reaches 37 c. c. at 25 mm. of arterial pressure. The curve of the general empirical formula is definitely higher than the inspected curve although it is approximately correct for the higher blood pressures.

Figure 5 shows the relationship of blood pressure to the efflux of blood when a cannula with an outlet area of 7.548 sq. mm. was employed. Four dogs weighing 12.3, 22.7, 20.4 and 27.3 kg., respectively, were used. The individual cases are scattered in this figure although the central tendency is quite obvious and is expressed by the curve drawn by inspection. This curve shows that 220 c. c. of blood leave the cannula in ten seconds of time when the blood pressure is 159 mm. of Hg. The curve descends steadily to 37 c. c. of blood outflow at 25 mm. of arterial pressure. The curve drawn by the general empirical formula is slightly higher than that drawn by inspection.

The experiments set forth in Figure 6 were made on three dogs weighing 26.4, 20.0 and 25.1 kg., respectively. The cannula used to drain off the blood had a cross section area of 9.512 sq. mm. The central tendency of the individual cases in this figure is expressed by the inspected curve. This curve shows that 200 c. c. of blood flows from the cannula in ten seconds when the arterial pressure is 135 mm. of Hg. and that the amount of blood outflow per ten seconds of time descends steadily to the amount of 35 c. c. at a blood pressure of 25 mm. of Hg.

The absolute data for each experiment are summarized in Table 1. The number of observations on each dog and the number of experiments for each figure are given. The body weight of the dog before

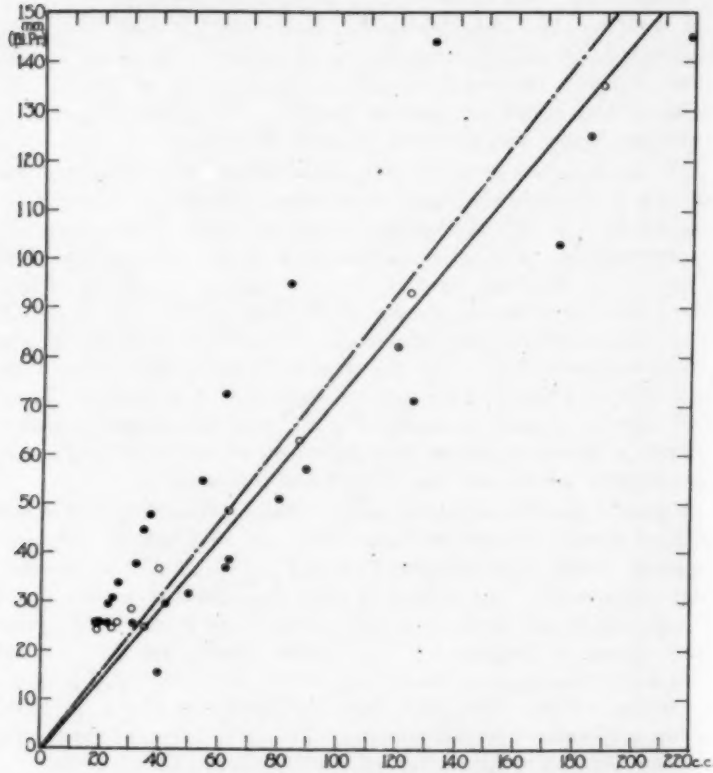

Fig. 5.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had an outlet 7.548 sq. mm. in area. Abscissa: efflux of blood in c.c. per 10 seconds of time. Ordinate: blood pressure in mm. of Hg. Individual cases are indicated by solid dots (for Experiment 12), by circle-crosses (for Experiment 13), by open circles (for Experiment 14) and by circle-dots (for Experiment 15). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.)=0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

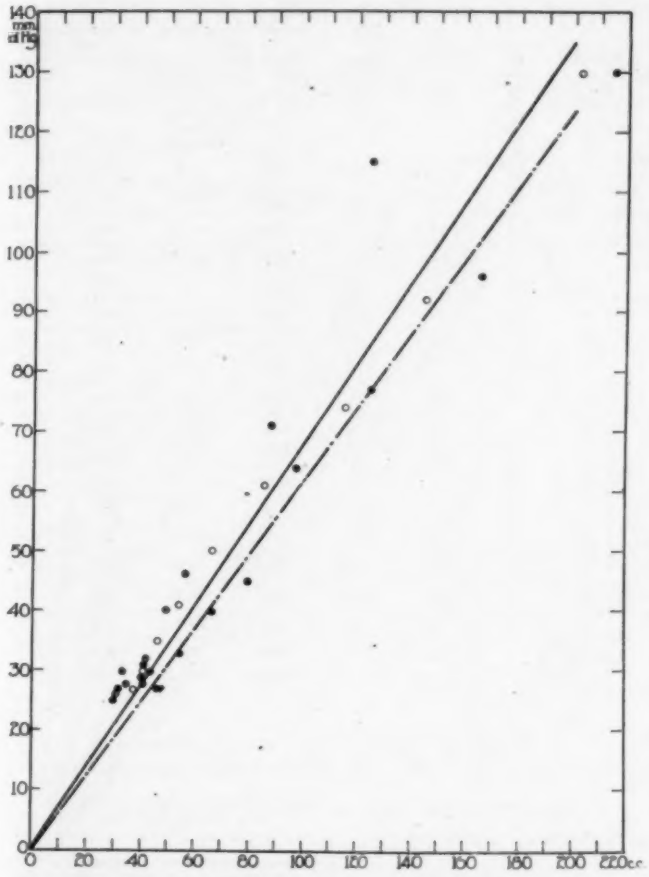

Fig. 6.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had an outlet 9.512 sq. mm. in area. Abscissa: efflux of blood in c.c. per 10 seconds of time. Ordinate: blood pressure in mm. of Hg. Individual cases are indicated by solid dots (for Experiment 16), by circle-crosses (for Experiment 17) and by open circles (for Experiment 18). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.) = 0.17 (area [sq. mm]) (blood pressure [mm. Hg.]).

TABLE 1.—Absolute Data for Individual Experiments
Blood Volume (C.c.)=0.17 (Area [Sq. Mm.]) (Blood Pressure [Mm. of Hg.])

Number of Graph	Number of Experiment	Number of Observations in Experiment	Weight of Dog, Kg.	Total Volume of Blood, C.c.	Average Blood Flow, C.c.		Average Blood Pressure, Mm. of Hg	
					Observed	Calculated from Observed Average Blood Pressure	Observed	Calculated from Observed Average Blood Flow
1	1	13	4.54	200	10.30	10.58	55.0	54.0
	2	20	4.54	234	10.05	10.98	57.2	52.3
2	3	6	5.67	329	22.30	16.30	40.3	55.4
	4	19	13.40	806	33.60	27.85	69.0	82.5
	5	9	7.72	381	28.30	31.12	77.0	70.3
3	6	12	9.54	488	31.40	27.35	44.7	51.4
	7	17	20.45	1,074	52.00	47.90	78.3	84.7
	8	15	15.20	825	46.40	36.90	60.4	75.8
4	9	17	28.10	1,333	61.70	55.50	54.0	59.7
	10	6	10.13	408	50.70	47.40	45.8	49.0
	11	11	21.8	1,215	75.50	72.10	69.8	73.0
5	12	11	12.3	632	48.00	71.90	56.0	36.9
	13	7	22.7	948	83.00	69.40	54.0	64.8
	14	9	20.4	700	67.00	68.50	53.4	52.4
	15	9	27.3	1,394	86.10	78.40	57.2	67.2
6	16	14	26.4	1,509	77.60	78.40	48.5	48.0
	17	9	20.2	737	56.20	75.0	46.4	34.8
	18	9	25.1	1,206	88.30	97.0	60.0	54.6

TABLE 2.—Absolute Data for Each Graph
Blood Volume (C.c.)=0.17 (Area [Sq. Mm.]) (Blood Pressure [Mm. of Hg.])

$$\text{Blood Pressure (Mm. of Hg.)} = \frac{\text{Blood Volume (C.c.)}}{0.17 \text{ Area (Sq. Mm.)}}$$

Numbers of Graphs	Cannula			Average Blood Flow, C.c.		Average Blood Pressure, Mm. of Hg	
	Radius of Lumen, Mm.	Area of Lumen, Sq. Mm.	Approximate Gage	Observed	Calculated from Observed Average Blood Pressure	Observed	Calculated from Observed Average Blood Volume
1 and 2	0.60	1.131	16	10.2	10.8	56.2	53.0
3 and 4	0.87	2.378	14	30.2	26.7	66.1	74.7
5 and 6	1.07	3.597	13	44.4	38.6	62.0	72.5
7 and 8	1.39	6.070	11	64.2	59.5	57.6	62.2
9 and 10	1.55	7.548	—	69.1	70.9	55.2	53.7
11 and 12	1.74	9.512	—	74.6	82.6	51.1	46.1

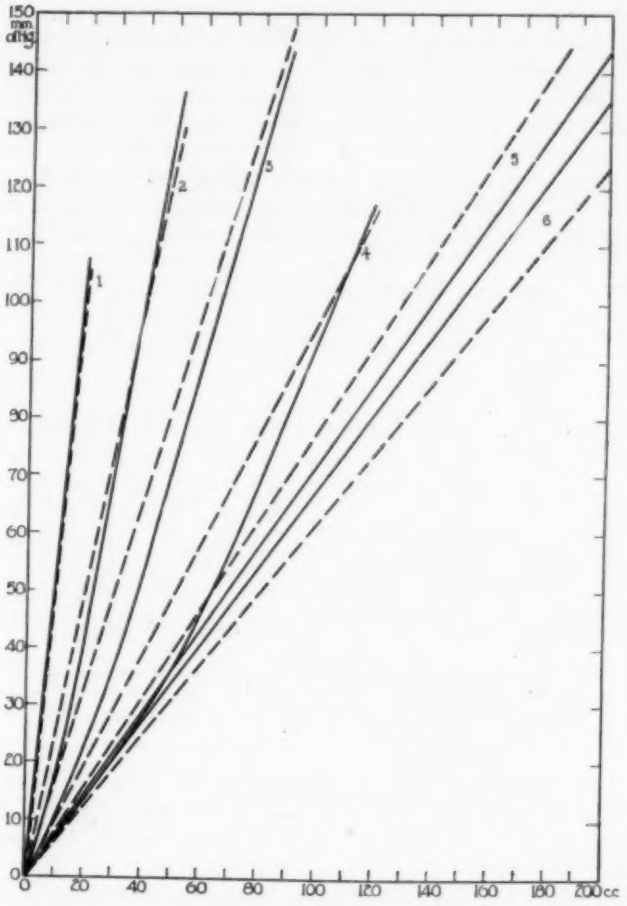

Fig. 7.—A series of curves illustrating the relationship between blood pressure and the efflux of blood per 10 seconds of time. These curves are taken from Figures 1, 2, 3, 4, 5 and 6. Abscissa: Blood flow in c.c. per 10 seconds. Ordinate: blood pressure in mm. of Hg. The solid lines indicates curves drawn by inspection. The broken lines are curves drawn to the general empirical formula: Blood flow (c.c.)=0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

the operation is indicated in kilograms and the total amount of blood drained from the arteries during the experiment is noted in c. c.

2. An enumeration of arithmetic means obtained from this data has been carried out for the individual experiments (Table 1) and for these experiments grouped according to the cannula used (Table 2).

3. A comparison of the observed and the calculated absolute values can be made by a survey of the collected absolute curves (Fig. 7) or by inspection of the adjoining columns of observed and calculated determinations in Figures 1 and 2.

4. The curves taken from the field graphs are collected for the purpose of comparison in Figure 7. Considering the variability of the blood pressure due to experimental error, the inspected curves from

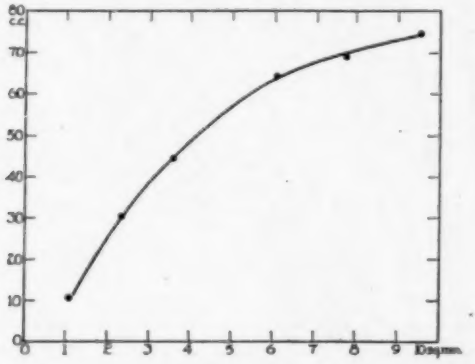

Fig. 8.—A curve to show the relationship between blood flow and the size of the cannula outlet. Abscissa: average efflux of blood in c.c. per 10 seconds of time. Ordinate: the area of the cannula outlet in sq. mm. The solid line is a curve smoothed by inspection.

four field graphs (Fig. 1, 2, 5 and 6) fit closely the general empirical formula. The inspected and the absolute curves from Figures 3 and 4, however, show a marked deviation, especially in the intermediate values of the curve.

In Table 1 the observed absolute values of both blood flow and blood pressure can be compared to the calculated values of blood flow and blood pressure respectively.

Table 2 demonstrates the correlation of the observed blood flow and the observed blood pressure with the respective calculated blood flow and blood pressure values.

5. The significance of the relationship between blood flow and the size of the cannula outlet is portrayed in Table 2 and Figure 8. The absolute averages of observed blood flow per ten seconds of time (Table 2) increases with the size of the cannula. In Figure 8 this

relationship is expressed graphically. The abscissa represents the cross section area of the opening of the cannula in sq. mm.; the ordinate gives the average efflux of blood per ten seconds of time. The curve based on this absolute data is logarithmic in type. The amount of blood flowing from the cannula in a given length of time increases rapidly at first as a larger cannula is used. When cannula gage 11 is employed (which has a cross section area of 6.07 sq. mm.) the blood flow per unit of time increases at a slower rate. The efflux of blood reaches a maximum average quantity of 75 c. c. per ten seconds when a cannula, 9.512 sq. mm. in area, is used.

The significance of this relationship between the flow of blood and the lumen of a cannula is not understood at the present time. It may be explained in several ways, none of them entirely satisfactory. At any rate, the general empirical formula is definitely influenced by this factor. A point is reached at which the size of the cannula makes little difference in the amount of blood flowing from an artery.

SUMMARY

The relationship of the blood pressure, the efflux of blood from the carotid artery of a dog, and the lumen of a cannula, the cross-section area of which ranges between 1 and 10 sq. mm., can be expressed by the general empirical formula:

Blood flow (c. c.)=0.17 (Area [sq. mm.]) (Blood pressure [mm. Hg.]).

STUDY OF BLOOD SUGAR CURVES FOLLOWING A STANDARDIZED GLUCOSE MEAL*

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ST. LOUIS

The following study is concerned with the effort to demonstrate the main factors which influence the duration of hyperglycemia after a glucose meal. More than 200 cases have been studied critically. There is extensive literature on the subject of blood sugar curves after various sorts of carbohydrate meals. In some studies standardized meals were given, in others not. Many clinicians have assigned diagnostic importance to an increased hyperglycemia following glucose ingestion.

The interpretation of the value of sugar curves depends on the following factors: (1) The technic of the administration of the glucose meal; (2) the collection of blood samples; (3) the method of doing the blood sugar determination, and (4) the wide application of the test so as to learn the many factors which influence these curves.

We believe it necessary, in order to support our conclusions, to discuss the first three of these points in detail.

Standardized Glucose Meal.—The standardized Janney[1] glucose meal was used. Glucose is the sugar of choice because it is most readily absorbed and because there are data as to the rate of its absorption from the gastro-intestinal tract. Fisher and Wishart[2] and Janney[3] have shown, by different methods, that from 66 to 80 per cent. of injected glucose is absorbed in the course of two hours.

The question of absorption is an important one. The curves here studied would indicate that absorption is fairly constant for the individual. This is brought out by the similarity of repeated curves (Table 1) on the same individual. The constancy of these curves is rather striking, especially where the symptoms and signs have not greatly changed. It is probable, therefore, that the absorption rate is fairly constant, at least for each individual. Again, in analyzing two hundred curves only six were found with a sudden increase in hyperglycemia at the end of the second hour, there having been no hyperglycemia the first hour. In other words, nearly all curves reach the maximum at the end of the first hour and the second hour levels are usually lower, or only slightly higher, than the first hour ones. This would show that absorption is quite rapid.

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1. Janney: Proc. Soc. Exper. Biol. & Med. **15**: 1917-1918. Janney and Isaacson: J. A. M. A. **70**:1131 (April 20) 1918.
2. Fisher & Wishart: J. Biol. Chem. **13**:49, 1912.
3. Janney: J. Biol. Chem. **22**:191, 1915.

Sansum and Woodyatt [4] have shown that the maximum intravenous tolerance rate of man and animals without glycosuria is 0.85 gm. per hour per kilo of weight. Intravenous tolerance methods, although scientifically desirable, are not practical. The known facts for determining a standard alimentary dose are: The above noted intravenous tolerance and the average absorption rate of 66 per cent. in two hours. The theoretical dose would be $(2 \times 0.85 \times \frac{100}{66})$ or about 2.5 gm. sugar per kilo. Janney has recommended 1.75 gm. per kilo as a

TABLE 1.—Repeated Curves

Diagnosis	Date	Blood Sugar Values, per Cent.				Curve Classification
		Fasting	1st Hr.	2d Hr.	3d Hr.	
Dyspituitarism	12/21/20	0.092	0.124	0.085	0.075	S
	2/ 4/21	0.092	0.120	0.085	0.082	S
Neuritis of sciatic nerve	2/ 8/21	0.085	0.190	0.150	0.130	III
	2/14/21	0.085	0.185	0.175	0.150	III
Hypothyroidism	10/14/20	0.090	0.110	0.095	0.095	S
	10/19/20	0.090	0.110	0.085	0.095	S
Manic-depressive psychosis	12/13/20	0.090	0.160	0.170	0.140	III
	1/10/21	0.100	0.182	0.195	0.175	III
	1/20/21	0.140	0.192	0.140	0.140	III
Lethargic encephalitis	12/ 8/20	0.100	0.110	0.090	0.080	S
	12/13/20	0.090	0.087	0.080	0.090	S
Exophthalmic goiter	6/ /20	0.168	0.280	0.220	0.113	II
	10/27/20	0.175	0.440	0.220	0.095	II

TABLE 2.—Showing Composition of Glucose Meal

Weight, Pounds	Glucose, Gm.	Lemon Juice, C.c.	Water, C.c.
90	72	54	126
100	80	60	140
110	88	66	154
120	96	72	168
130	104	78	172
140	112	84	196
150	120	90	210
160	128	96	224
170	136	102	238
180	144	108	252
190	152	114	266
200	160	120	280
210	168	126	294
220	176	132	308
230	184	138	322
240	192	144	336

standard dose. This amount of glucose for a man weighing 150 pounds, for instance, would amount to 120 gm. of glucose, or 480 calories. Such a man in basal state plus 10 per cent. increase for the specific dynamic action of glucose would be burning from 70 to 75 calories per hour. This dosage of glucose is, therefore, greatly in excess of caloric needs under ordinary circumstances and would show, with an absorption efficiency of 66 per cent., the glycogenic function of the individual or his ability to store the excess of an amount of sugar, commensurate

4. Sansum and Woodyatt: J. Biol. Chem. **30**:155, 1917.

with his weight, absorbed in a unit of time. Sansum and Woodyatt [4] have also shown that injecting animals in excess of the tolerance rate with varying concentrations of glucose made no difference in the amount of glucose in the urine, but that it did make a difference in the height of the blood sugar. It is, therefore, better technic to use a 40 per cent. solution of glucose using water and lemon juice as a solvent.

It seems obvious that one should not give 100 gm. glucose to an individual weighing 200 pounds and a like amount to one weighing 100 pounds and expect duplicate results in blood sugar concentration. It has been fairly well established that blood volume varies approximately with weight. Normally sugar is stored both in the liver and in the muscles. Palmer [5] found that in the diabetic animal the amount of glucose in the tissues varied with the hyperglycemia. It is possible, therefore, that sugar storage might take place in some abnormal conditions in other tissues besides the liver and muscles, and it would seem that the weight of the individual is our best index to his available space for storing glucose.

TABLE 3.—Showing the Absence of Relationship Between Weight and the Type of Curve

Weight in Pounds *	Number of Individuals	
	Normal Curve	Subnormal Curve
90–100	4	3
100–110	8	5
110–120	2	6
120–130	6	5
130–140	6	2
140–150	6	5
150–160	2	2
160–180	1	2
180–200	5	2
200 plus	2	

* What the average weight of all hospital patients is, is not known, but the table shows the size of the patient does not influence the curve.

In some of the latest work in blood sugar determinations [6] after a glucose meal, a constant amount of glucose was used for all individuals. The results would have been more constant if the weight of the individuals had been taken into consideration (Table 3). The same can be said for the amount of water given with the meal.

Blood Sugar Determinations.—The blood was drawn with a 5 or 10 c.c. syringe and introduced into a test tube containing a few crystals of potassium oxalate and gently shaken. The first specimen was taken with the patient in a basal state, twelve hours after the last food. After the collection of the blood, the standardized meal was given. The blood was drawn again at the end of one, two and three hours. The third hour specimen was found to be of great importance. It is necessary that the blood should be precipitated immediately after taking the sample.

5. Palmer: J. Biol. Chem. **30**:79, 1917.

6. Allen, Wishart and Smith: Arch. Int. Med. **24**:523 (Oct.) 1919. Boothby: J. A. M. A. **77**:252 (July 23) 1921.

Meyers and Bailey's[7] modification of Benedict's first method was used: 3 c.c. blood was added to 12 c.c. saturated picric acid solution and a few crystals of picric acid. The blood was thoroughly shaken and filtered after five minutes. The standard glucose solution was made up of 1 mg. glucose to 5

TABLE 4.—Comparison of Blood Sugar Values by Benedict's and Shaffer's Methods

Case	Fasting 1st, 2d and 3d Hours		Classification	
	Benedict's Method, per Cent.	Shaffer's Method, per Cent.	By Benedict	By Shaffer
1	0.089 0.135 0.123 0.109	0.077 0.149 0.125 0.064	N*	N
2	0.087 0.159 0.136 0.117	0.096 0.171 0.143 0.125	II	II
3	0.103 0.169 0.135 0.095	0.088 0.138 0.119 0.074	N	N
4	0.104 0.089 0.113 0.064	0.096 0.090 0.099 0.095	S	S
5	0.088 0.168 0.150 0.117	0.099 0.143 0.138 0.127	II	III
6	0.095 0.148 0.167 0.137	0.090 0.157 0.166 0.109	III	II
7	0.143 0.195 0.138 0.142	0.115 0.195 0.142 0.114	III	III
8	0.098 0.190 0.200	0.099 0.176 0.181	III ?	III ?
9	0.102 0.096 0.088	0.095 0.082 0.088	S	S
10	0.089 0.118 0.091	0.079 0.106 0.093	S	S
11	0.126 0.236 0.154 0.139	0.113 0.191 0.156 0.135	III	III
12	0.082 0.224 0.226 0.143	0.072 0.230 0.189 0.101	III	II

* N, normal; S, subnormal; II, 2 hour sustained; III, 3 hour sustained.

c.c. saturated picric acid; this solution being part of the same sample of saturated picric acid that was used to precipitate the blood.

Cowie and Parsons[8] have shown how much more sensitive picric acid solutions are to such substances as acetone, diacetic acid and epinephrin than

7. Meyers and Bailey: J. Biol. Chem. **24**:147, 1916.
8. Cowie and Parsons: Arch. Int. Med. **26**:333 (Sept.) 1920.

to sugar itself. This work explains the very high blood sugars obtained in the cases of diabetes mellitus, but in the absence of acetone bodies the method is fairly accurate.

Since the publication by Shaffer and Hartmann[9] of their iodometric method, a considerable number of curves have been determined by both methods. In only minor respects has the classification of curves been changed by values obtained by the Shaffer method. In fifty blood sugar determinations done by both methods varying from 0.06 to 0.30 per cent., the averages at different levels by the two methods agree within a few per cent.

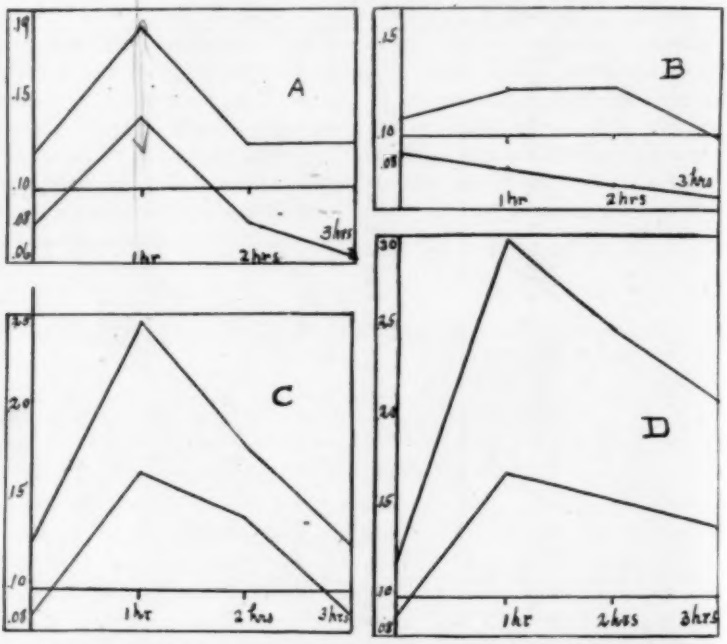

Fig. 1.—In each curve the two lines represent the limits between which the curves of that type falls. Ordinates show percentage of blood sugar. A, Normal curve; B, subnormal curve; C, Type II curve; D, Type III curve.

Classification of Curves.—In dealing with a considerable number of curves some sort of classification is necessary. This introduces the question of terminology. Sugar tolerance work began by feeding sugar by mouth and watching for its appearance in the urine. If an individual could take 100 gm. glucose and show no sugar in his urine, his "tolerance" would be considered normal; if he could take more than 100 gm. without glycosuria his "tolerance" was increased, and if he showed glycosuria on taking 100 gm. his "tolerance" was decreased.

9. Shaffer and Hartmann: J. Biol. Chem. **45**:365, 1921.

It is impossible to transpose this term "tolerance" into the terminology of blood sugar because a higher "tolerance" means a low blood sugar curve and a low "tolerance" means a high blood sugar curve. It has been our experience that the use of the word "tolerance" only leads to confusion and it would, therefore, seem to be better to use the term "blood sugar curve after glucose meal" or "blood glucose curve."

In consideration of the classification of curves it has not been considered important to include fasting hyperglycemia because it has been found that a fasting hyperglycemia is not a common condition, except where there is a loss of power to oxidize glucose, or in the presence of ashyxia or severe toxemia. As a rule, fasting hyperglycemia has not been found in endocrine or neurologic cases.

Normal curves were constructed on five normal individuals and also on about forty patients in the hospital who showed no demonstrable cause for a disturbed glycogenic function. These normal curves agree with those of other observers[10] in that after the normal fasting level there is a hyperglycemia at the end of the first hour of from 0.14 to 0.19 per cent. and at the end of the second hour the blood sugar level is within normal limits, or from 0.08 to 0.12 per cent. The third hour is still within normal limits from 0.06 to 0.12 per cent. We have assumed a higher normal hyperglycemia at the end of the first hour than other observers. However, this seemed justified when the procedure was so well controlled and the clinical data carefully studied. Many of the normal curves show a marked hypoglycemia at the end of the second and third hours. This hypoglycemia may be to the extent of from 0.06 to 0.08 values—so low that mere changes in blood volume would scarcely account for them. We cannot offer an explanation but have observations to show that by the end of the fourth hour the blood sugar values return to normal levels.

Abnormal curves have been divided into two main classes. The sustained curve, showing an abnormally sustained hyperglycemia, and the subnormal curve, which shows no normal hyperglycemia and even a hypoglycemia after a glucose meal. The curves showing sustained hyperglycemia we have divided into two groups: those showing hyperglycemia the second hour but with a return to normal levels the third hour; and those showing hyperglycemia at the end of three hours. The reason for this division of sustained curves into two groups will appear later.

Subnormal curves show a hypoglycemia or a normal fasting blood sugar. No hyperglycemia follows the administration of a glucose meal. The failure of the appearance of hyperglycemia may be due to one or both of two possibilities: Either a delayed absorption rate or an

10. Hammon and Hirschman: Arch. Int. Med. **20**:761 (Dec.) 1917.

increased glycogenic function. There are data [11] to show that in one condition, hypothyroidism, there is no delayed absorption in spite of the subnormal curves. Delayed absorption may occur in some conditions, such as hypopituitarism.

DISCUSSION OF MATERIAL

In the cases studied we noted age; weight; pulse rate and temperature; diagnosis (as obtained from the history sheet); gonads; children; menses; sexual power and desire; sympathetic symptoms; sweating; vasomotor instability; emotional tendencies, fear, anxiety; reflex excitability; gastro-intestinal symptoms; pituitary: sella (roentgen ray); bones; hair; eyegrounds; visual fields; secondary sexual characters; thyroid: vascular activity in gland itself; tremor; external ocular movements; size; exophthalmos; skin; special tests: basal metabolism; goetsch; hemoglobin.

In this study emphasis has been laid particularly in the selection of cases, on the so-called suspected endocrine disturbances of the thyroid and the pituitary; on the fatigued states, and on the hysterias and true dementias.

Many other conditions show abnormal curves, but the nature and constancy of their influence on the glycogenic function is even more uncertain than the above mentioned conditions. Such conditions are any mild toxemia, such as that in low grade bacterial infection; malignancy, etc., acidosis of any origin; drugs, such as opium and its derivatives, or salicylates. It is probable that these conditions can disturb blood sugar curves; certainly they affect general metabolism to some degree.

In this type of case the curves presented are not as numerous as one would wish. A few furunculosis cases (Fig. 2) show sustained curves. Some carcinomas of the gastro-intestinal tract, especially when metastases have taken place, show the same curve. Others with localized carcinoma show a normal curve. A normal curve is usually found in arthritis, but in the presence of fever or after foreign protein injections there is a high curve. If sugar curves are to be of value from an endocrine or a neurologic point of view, such conditions as may disturb glycogenic function should be avoided. Too little is known about them and there is no reason to believe their influence on the glycogenic function is a constant one. It seems more probable that a sustained curve in such conditions is a part of the general effect of incidental toxemia rather than a specific characteristic of a definite metabolic disturbance.

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11. Janney and Isaacson: Arch. Int. Med. **22**:160 (Aug.) 1918. Janney and Henderson, Arch. Int. Med. **26**:297 (Sept.) 1920.

Focal Infection.—Pemberton [12] has shown the effects of low grade inflammatory infection on delaying glycogenesis. Not only in cases of arthitis, but in other focal inflammatory processes, he found higher curves than in his normals. He did not use the standardized glucose meal. In a few cases he observed a return to normal curves after the removal of the foci of infection.

The manner in which toxins may influence the height of blood sugar curves is open to much speculation.

1. The toxin may directly stimulate the action of the diastase of the liver and muscles, or it may inhibit their glycogenic power.[13] Langfeldt [14] has recently shown in vitro the optimum p_H at which liver diastase works in the presence of thyroid extract and epinephrin. Toxins from foci may possibly disturb the hepatic acid-base equilibrium.

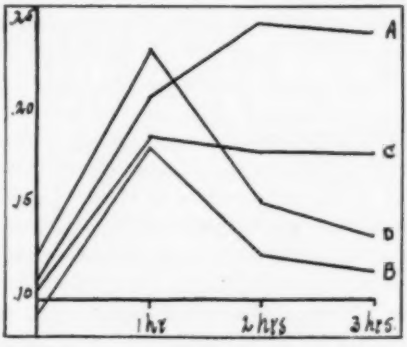

Fig. 2.—A and B curves are of arthritis cases. Curve A was taken two days following the intravenous injection of foreign protein. B, normal curve obtained in most cases of arthritis. C and D, curves of cases of furunculosis.

2. Focal toxins may act on glycogenolysis through their effect on suprarenal medulla directly or through autonomic reflex.

3. Focal toxins may also act on higher cerebral centers.

The association of fatigued state with focal infection is often noted. The curves of such conditions will be discussed later. Again, the focal toxins may disturb the mixture of food stuffs burned in the cell. The well known protein-sparing property of carbohydrate, especially in long sustained fevers, suggests that carbohydrate is burned most readily and possibly is mobilized to protect protein. The possibilities of the effects of toxins on glycogenesis and glycogenolysis have not

12. Pemberton and Foster: Arch. Int. Med. **25**:243 (Feb.) 1920.
13. Lusk: Science of Nutrition, p. 522, quoting Rosenthal, who showed that injection of diphtheria toxin prevented glycogen formation.
14. Langfeldt: J. Biol. Chem. **46**:381, 1921.

been exhausted, but enough has been mentioned to show the complexities of the possibilities. Certainly at present it is better to suppose that disturbance of glycogenic function in focal infection is a manifestation of the effects of infection just as hyperpyrexia or esthenia. The rationale of restricted diet in these cases can be questioned: Why deprive these patients of the protein sparing property of carbohydrate? Why feed typhoid fever patients carbohydrate and deny it to the arthitic? The great losses of weight seen in chronic arthitis would suggest that such patients are greatly in need of carbohydrate in abundance. The metabolism of arthitis does not differ from that of any other chronic focal infection. Certainly there is no loss of power to oxidize glucose, nor is there reason to believe that products of carbohydrate oxidation have a deleterious effect on periarticular inflammatory processes. Even if the toxins of the agent of infectious arthitis do cause sugar mobilization, that in itself should not suggest carbohydrate denial as a therapeutic indication. The experience of this clinic with low carbohydrate diet in arthitis has been quite disappointing.

Thyroid Diseases.—The influence of the thyroid gland on sugar curves has long been appreciated. The internal secretion of the thyroid excites two influences: (1) the delaying of glycogenesis, or an increased glycogenolysis; (2) an increased or stimulated metabolism.

When thyroid is fed carbohydrate is burned rapidly. One would therefore suppose that curves of exophthalmic goiter patients (Fig. 3) would be high but fall quickly, the rapid fall being associated with the increased metabolism. This is brought out by the fact that in spite of the height of the curves, normal blood sugar levels were reached by the end of three hours. Basal metabolism was performed on many cases. As found by Janney, there is no relationship between the height of metabolism and the height of the blood glucose curve. If the metabolism were extremely high one would suppose that the glycogen stores would be exhausted continually and the sugar, which with a lower metabolism would remain mobilized, is burned up; the result being a lower curve than is found in milder cases. We found this to be the case. One of the lowest curves in Figure 3 is from a patient having a basal rate of + 100 per cent. The reverse also is true; patients showing the highest curves had basal rates of about + 50 per cent.

The curves in exophthalmic goiter cases clearly indicate the nature of the dietetic treatment of hyperthyroidism: (1) To protect protein, a high carbohydrate intake; (2) to avoid hyperglycemia, the feeding in hyperthyroid cases should consist of many and small meals.

With clinical evidence of lack of thyroid secretion, curves were obtained which substantiate those already published [11] (Fig. 4). Janney did not find the constancy in hypoglycemia after the glucose meal that is shown in Figure 4. Cases under treatment are not included in this

chart. In some cases the curves very quickly become high under treatment, while others remain low. It has been shown experimentally in animals whose thyroids have been removed that there is no delay in intestinal absorption.[11] If this be true, the low curves in hypothyroidism must be due to increased sugar storage.

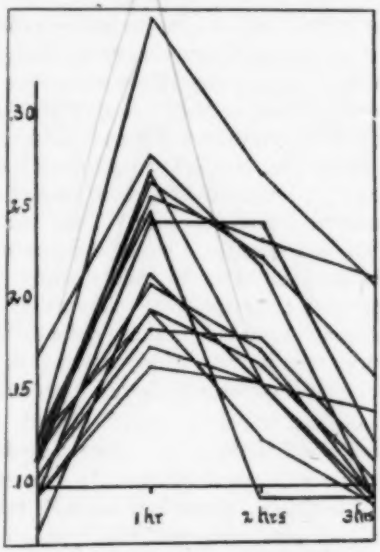

Fig. 3.—Curves of hyperthyroidism.

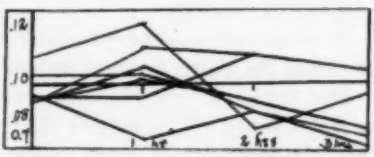

Fig. 4.—Curves of hypothyroidism.

Pituitary Cases.—The posterior lobe of the pituitary gland has been shown to affect the glycogenic function;[15] in acromegaly there is a low "tolerance" while in hypopituitary disease the "tolerance" is high.[16] Glycosuria following experimental stimulation of the pituitary has been shown to take place reflexly to the splanchnic area and also after all known nervous paths have been cut, indicating a true hormone glycogenolysis. No cases have been observed clinically or metabolically

15. Cushing: The Pituitary Body and Its Disorders, Lippincott, 1911.
16. Weed, Cushing and Jacobson: Bull. Johns Hopkins Hosp. **24**:40, 1913.

showing high curves, but a large number of cases diagnosed "hypopituitarism," "dyspituitarism" and "polyglandular syndrome" show low curves. It is in this type of case that the factor of delayed absorption may play a part. We have observed delayed water absorption in some of these cases.

Mild Diabetes.—The necessity of pancreatic hormone for glycogen formation was early demonstrated in perfusion experiments.[14] It is not known whether an increased secretion by the islands of Langerhans ever occurs, but a decrease in pancreatic hormone has two effects; loss of glycogenic power and loss of ability to oxidize glucose. It would, therefore, be reasonable to suppose that even if there is loss of oxidative power to a small degree, or, in other words, a very mild diabetes, the hyperglycemia would be sustained to a more marked degree than any other condition affecting glycogenesis.[10] That such is the case is shown by the curves in Figure 5. One of the greatest uses for blood sugar curves is in doubtful cases of mild diabetes. With a normal fasting blood sugar and a carbohydrate tolerance of from 150 to 200 gm. the curves following a glucose meal are quite distinctive, and differ from any other curve seen in cases of glycosuria. At the end of three hours the hyperglycemia is commonly above 0.3 per cent.

Renal Diabetes.—The so-called "renal" diabetic shows glycosuria with normal fasting blood sugar levels. Two cases have been studied carefully. Both gave subnormal curves. In one case the threshold glycemia seemed to be 0.075. Great care must be taken to distinguish between the emotional glycosuria and this type of glycosuria. The emotional patient's curve rises to above normal limits the first hour and may be sustained still longer. The curves of the "renal diabetic" here observed are quite flat (Fig. 5).

Mental States.—It is not proposed here to enter into discussion as to whether disturbances of the higher cerebral centers act on glycogenic function through reflex action on the chromafin-sympathetic system. It is simpler to accept Cannon's [17] hypothesis that there is a reflex stimulation of epinephrin formation in some mental conditions. The purpose here is to make clear the very considerable influence of various disturbances of the mental state on blood sugar curves. There is, however, one condition which would give distinct evidence of the effect of suprarenal medulla on sugar curves; namely, Addison's disease. With hypofunction of the suprarenal medulla and the absence of other factors influencing them, low curves should be obtained. Two cases have been followed for several months. The first patient had tuberculosis of the lungs and gave a normal curve; the second patient,

17. Cannon: Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton, 1920.

the pathology of whose suprarenal was unknown, gave a subnormal curve (Fig. 6). The first case shows the effect of the bacterial intoxication as well as the deficiency of medullary-adrenal secretion.

Cannon found that pain, rage and fear in animals caused, in a considerable number of cases, the appearance of glycosuria. The same

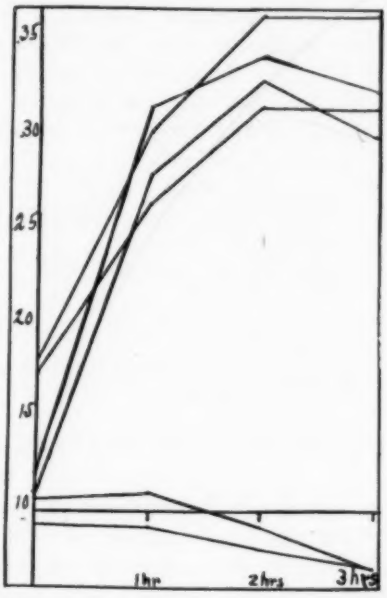

Fig. 5.—The upper curves are those of mild cases of diabetes mellitus. Compare with Figures 3 and 8. The lower curves are of "renal" diabetes. Compare with Figures 7 and 8.

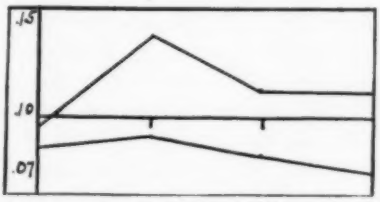

Fig. 6.—Curves of two cases of Addison's disease. The upper of the two is from a patient who had an active tuberculous lesion which would tend to raise the curve.

has been observed in man, especially in states of excitement and after severe mental effort. We have studied the blood sugar curves of a considerable number of cases diagnosed as neurasthenia after a search was made for organic lesions; cases of hypochondriasis; hysteria;

epilepsy, both of organic origin and ordinary type; dementia praecox and manic depressive insanity,[18] and the outstanding fact is that no prediction can be made as to the nature of the curve from diagnosis alone. It may be possible for the psychiatrist or neurologist to determine what the particular mental condition is that stimulates glycogenolysis. Some of the interesting facts are as follows:

Hysterical individuals usually give a normal curve (Fig. 7) in spite of their intense emotional state. Hypochondriacs and manic depressive patients (Fig. 8) show, in the majority of cases, high curves. Neurasthenics and dementia praecox patients may show any type of curve. The uncertainty of the response in these cases makes the interpretation of blood sugar curves difficult.

Summary of Factors Influencing Curves.—To summarize these factors influencing glycogenesis and glycogenolysis in muscle and liver the following outline may help.

Glycogenesis; necessary hormones:

1. Pancreas,
2. Parathyroid (?)

Glycogenolysis; increased by:

1. Increased p_H of muscle, liver or blood. Found in such pathologic conditions as starvation acidosis, nephritic acidosis, etc.
2. Increased secretion of thyroid hormone.
3. Increased secretion of pars nervosa of the pituitary.
4. Increased activity of sympathetic-chromafin system may occur with:
   (*a*) Reflex stimulation from cerebral, peripheral or splanchnic areas.
   (*b*) Blood born stimuli, such as infections, malignant, in pernicious anemia, leukemia, etc.
5. Substances in the blood acting directly on glycogen stores in the muscles and liver, such as any of 4b.

So far as known the pancreas has the most definite and profound influence on formation of the glycogen. The evidence for the parathyroids lies in the fact that their removal causes glycosuria.[19] There seem to be many more factors stimulating sugar mobilization. Anything increasing H ion concentration of blood or locally in the tissues seems to stimulate glycogenolysis. This has been shown by intravenous injections of acids and in perfusion experiments.

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18. For permission to study these cases we are indebted to Prof. Sidney I. Schwab.

19. Underhill and Hilditch: Am. J. Physiol. **25**:66, 1909. Underhill and Blatherwick: Am. J. Chem. **18**:87, 1914.

The livers of experimental animals can be almost freed from glycogen by feeding thyroid.[20] Although respiratory quotients show no decrease in burning power for glucose during feeding,[21] it is undoubtedly the strongest stimulus known to sugar mobilization. The increased metabolism accompanying thyroid feeding tends to lessen

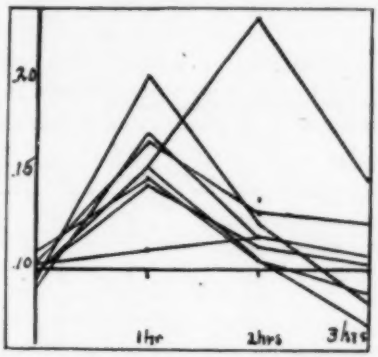

Fig. 7.—Cases of hysteria, many of which show intense emotional excitement. Seventy-five per cent. of uncomplicated cases of hysteria give normal curves.

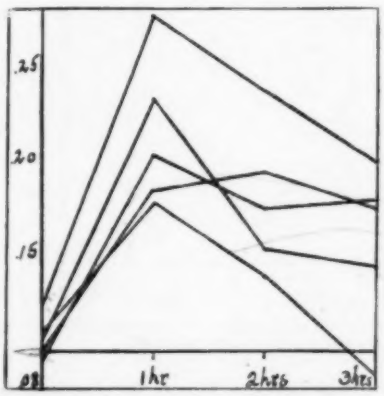

Fig. 8.—Cases of manic depressive insanity. Compare these curves with those of hyperthyroidism.

the glycemia by the rapid burning of sugar. Hyperthyroid blood sugar curves are high but steep, and show an interesting distinction from the high curves due to psychic disturbance which are not high but tend to be sustained. The explanation of increased glycogenesis when thyroid

20. Cramer and Krause: Quart. J. Exper. Physiol. **11**:59, 1917.
21. Cramer and McCall: Quart. J. Exper. Physiol. **12**:81, 1918.

hormone is decreased is only guesswork. If one considers the hormones of thyroid and suprarenal as opposed or balanced against the pancreatic hormone, disturbance of this balance increases or decreases glycogenesis. The increased glycogen storage coincident with thyroid deficiency might be taken as evidence that the pancreatic hormone overacts when not counterbalanced by thyroid.

TABLE 5.—SUMMARY OF CASES

Curves are classified thus: N, normal curve; S, subnormal curve; II, second hour sustained hyperglycemia; III, third hour sustained hyperglycemia. *

Diagnosis	Total No. of Cases	Curve Classification			
		N	II	III	S
Endocrine:					
Hyperthyroidism and exophthalmic goiter	19	1?	12	4	2?
Hypothyroidism and myxedema	10	1	0	0	9
Dyspituitarism; hypopituitarism; polyglandular syndrome	15	9	1	0	5
Addison's disease	2	1	0	0	1
Neurologic:					
Neurasthenia	15	4	4	2	5
Hysteria	16	8	1	3	4
Hypochondriasis	3	2	0	0	1
Organic Central Nervous System Lesions:					
Encephalitis	2	0	1	0	1
Tumor of brain (not pituitary)	4	2	1	0	1
Syphilis	9	4	2	2	1
Neuritis	2	0	1	1	0
Epilepsy	12	3	5	1	3
Constitutional inferiority	4	0	1	2	1
Psychoses:					
Dementia praecox	12	5	3	3	1
Manic depressive insanity	7	0	3	4	0
Senile dementia	2	0	0	2	0
Focal Infection:					
Arthritis, chronic	4	2	1	0	1
Arthritis, acute	1	0	0	1	0
Prostatitis, chronic	2	0	2	0	0
Appendicitis, chronic	2	2	0	0	0
Sinusitis	1	1	0	0	0
Keratitis	2	1	0	0	1
Furunculosis	2	0	0	2	0
Neoplasms:					
Carcinoma, stomach	1	0	1	0	0
Carcinoma, intestinal	2	1	1	0	0
Hodgkin's Disease	1	0	1	0	0
Miscellaneous:					
Goiter	3	3	0	0	0
Lead poisoning	1	0	1	0	0
Arteriosclerosis	..	0	2	1	0
Myocarditis	..	0	1	0	1
Nephritis	..	1	0	0	0

* Diagnoses with only one curve are not included.

In the above outline nervous effects on glycogenolysis are indicated as reflex through the agency of adrenalin. It must be borne in mind that this question is still a disputed one. It is also to be remembered that blood borne stimuli to glycogenolysis may act through adrenalin. These possibilities are quite hypothetical and are mentioned only as such. Again it is not known whether the many toxic substances disturbing the glycogenic balance toward the side of increased sugar mobilization act directly on the liver and muscles; on the nervous system or on the suprarenal medulla. All are possibilities.

CONCLUSIONS

1. The basis for the standardization of the technic of the administration of the glucose meal is pointed out. The necessity for such standardization is made clear.

2. The discussion of the many known factors which influence blood glucose curves shows the importance of the consideration of all of them when such curves form part of any study.

3. The pathologic conditions in which the form of blood glucose curve is usually (within certain limits) constant, are: (1) hyperthyroidism and hypothyroidism; (2) hypopituitarism, and (3) diabetes mellitus.

4. There are certain conditions which, in general, show increased curves after the glucose meal. The curves obtained in such conditions do not even approximate the fair degree of constancy found in the above mentioned conditions. Our present knowledge of glycogenic function in these conditions is rather meager. In this class belong the effects of infectious toxins; those of cancerous origin; those supposedly found in pernicious anemia and leukemia; Hodgkin's disease, etc. Here also belong conditions of the mental state. "Functional" disturbances, usually spoken of as neurasthenia, very definitely disturb the height of blood sugar after glucose meal.

CORRECTION

In the paper by Killian and Kast on "A Study of Significant Chemical Changes in the Blood Coincident with Malignant Tumors" in the ARCHIVES OF INTERNAL MEDICINE, December, 1921, the statement is made, page 813, that "the comparative decrease in the amounts of these (nonprotein nitrogen compounds) has been ascribed to an increased need for nitrogen for the new growth, whether it be malignant tumor or embryo." This statement follows a reference to the work of Theis and Stone, so that many would infer that the above explanation of the low nitrogen figures was offered by these writers. It should be stated that Theis and Stone offered no such explanation of the figures in this connection, but that the explanation was advanced by several workers verbally to us, and we inadvertently included it in our paper without proper explanation.

JOHN A. KILLIAN AND LUDWIG KAST.

BOOK REVIEWS

ACUTE EPIDEMIC ENCEPHALITIS (LETHARGIC ENCEPHALITIS). An Investigation by the Association for Research in Nervous and Mental Diseases. New York: Paul B. Hoeber, 1921. 258 pages, 36 illustrations. Price, $2.50.

This little book is worthy of attention for two important reasons: First, on account of its form, as it embodies a novel idea in the organization of centralized effort by a large body of investigators focused on one disease, and in the method of presentation of the subject to the reader. The book consists of the papers read at the first meeting of the Association for Research in Nervous and Mental Diseases held in New York in December, 1920, together with discussions and the final conclusions of a commission of distinguished neurologists who conducted the meeting and edited the book. At the meeting each reader of a paper was questioned by the commission to which the papers had been submitted beforehand. Anyone interested in the method of conducting scientific meetings and reporting their proceedings will be benefited by glancing over this volume, even if he is not especially interested in the subject.

Secondly, this is the first book which covers all phases of this new disease in a readable manner. The history of the disease, etiology, symptomatology, diagnosis and morbid anatomy are presented by well-known investigators. There are altogether thirty-six contributors but, thanks to the good editorial work of the commission, the subjects are presented in logical sequence and without needless repetition. A bibliography of eighteen pages of the most important articles is appended. As the literature already has grown to unwieldy proportions, the appearance of this book is timely, placing all essential data at the elbow of anyone desirous of authoritative and condensed information.

The commission which edited the book was composed of W. Timme, Pearce Bailey, L. F. Barker, C. L. Dana, Ramsay Hunt, Foster Kennedy, G. H. Kirby, H. T. Patrick, B. Sachs, W. G. Spiller, Israel Strauss, E. W. Taylor, F. Tilney and T. H. Weisenburg.

DIABETES: A HANDBOOK FOR PHYSICIANS AND THEIR PATIENTS. Philip Horowitz, M.D. Published by Paul B. Hoeber, New York. July, 1920. Pp. 1-186.

For convenience in handling his cases, the author has recognized four clinical types of diabetes, "mild, moderately severe, severe and juvenile." The diagnostic symptoms of each type are enumerated so that a given case of diabetes could readily be classified. The diet the author recommends is given, and the subsequent additions follow. The book contains very complete analytical tables showing the composition of foods, and lists of such ménus and recipes as are valuable in handling diabetics. In another chapter questions of hygiene and exercise are discussed briefly. The book is closed with a description of tests which are necessary in following intelligently the progress of the patient. No generalizations of the principles used in the formulation of the diets are given. Hence, the reader has no way of judging whether a given diet is adequate in protein or calories or whether the proper relationship between fats and carbohydrates has been maintained. It can be seen that such a collection of diets falls short of giving either the physician or patient an adequate conception of the fundamentals of diabetic management. Within the last year studies directed towards the rationalization of diet formulation have appeared. If these be accepted, then the present hand book may be regarded as out of date.

DISEASES OF THE DIGESTIVE ORGANS, WITH SPECIAL REFERENCE TO THEIR DIAGNOSIS AND TREATMENT. By CHARLES D. AARON, Sc.D., M.D., F.A.C.P. Lea & Febiger, 1921.

The third edition of this book is a comprehensive volume devoted to disorders of the entire gastro-intestinal tract—the plan of work following the physiologic path from the mouth downward. The usual diseases are treated clearly and fully, with full descriptions of the various laboratory and chemical procedures and their interpretation, many of which the general practitioner has never heard of—but with many of which he should be familiar. In general, the material is presented in a form resembling that of Osler's "Principles and Practice of Medicine," with definitions, etiology, pathology, symptoms, prognosis and treatment under separate headings. Colored plates, engravings and roentgenograms are used liberally to augment descriptions. Dietetic principles in health and disease, the high caloric feeding for typhoid; vitamins—their importance and distribution, and the functional disturbances of the nervous system, vagotonia and sympathecotonia, are clearly and fully discussed. Throughout the book are tables and paragraphs giving a type of information often desired and difficult to find—the analyses of various springs and waters, as compared with the more famous European Resorts; the composition of many proprietary preparations, both of food and from the various pharmaceutical houses. The book commends itself to both the specialist in diseases of the digestive tract and to the general practitioner and surgeon.